Reproductive Medicine Network

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PREGNANCY IN POLYCYSTIC OVARY SYNDROME II (PPCOS II): A 25 WEEK DOUBLE-BLIND RANDOMIZED TRIAL OF CLOMIPHENE CITRATE AND LETROZOLE FOR THE TREATMENT OF INFERTILITY IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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1 Acronyms

American College of Obstetricians and Gynecologists	ACOG	Identification	ID
Advisory Board	AB	Institutional Review Board	IRB
Adverse Event	AE	Intrauterine Fetal Demise	IUFD
Anti-Mullerian Hormone	AMH	Investigator Global Assessment (acne)	IGA
Aromatase Inhibitor	AI	Investigational New Drug	IND
Body Mass Index	BMI	Luteinizing Hormone	LH
Complete Blood Count	CBC	Ovarian Hyperstimulation Syndrome	OHSS
Clomiphene Citrate	CC	Polycystic Ovary	PCO
Case Report Form	CRF	Polycystic Ovary Syndrome	PCOS
Data Coordination Center	DCC	Progesterone	P4
Data and Safety Monitoring Board	DSMB	Principal Investigator (Site)	PI
Deoxyribonucleic Acid	DNA	Protected Health Information	PHI
Estradiol	E2	Pregnancy in Polycystic Ovary Syndrome Study	PPCOS
Free Androgen Index	FAI	Quality Control	QC
Ferriman Gallwey Score (hirsutism)	F-G	Quality of Life	QOL
Female Sexual Distress Scale	FSDS	Reproductive Medicine Network	RMN
Female Sexual Function Inventory	FSFI	Rate Ratio	RR
Follicle Stimulating Hormones	FSH	Serious Adverse Event	SAE
Food and Drug Administration	FDA	Steering Committee	SC
Good Clinical Practice	GCP	Specialized Cooperative Center Programs in Reproductive Research	SCCPIR
Hyperandrogenism	HA	Selective Estrogen Receptor Modulator	SERM
Human Chorionic Gonadotropin	hCG	Medical Outcomes Survey, Short Form 36	SF-36
Human Investigations Committee	HIC	Sex Hormone Binding Globulin	SHBG
Health Insurance Portability and Accountability Act	HIPAA	Testosterone	T

2 Study Synopsis

2.1 Objectives

To determine the safety and efficacy of clomiphene citrate, a selective estrogen receptor modulator, compared to letrozole, an aromatase inhibitor, in achieving live birth in infertile women with polycystic ovary syndrome (PCOS).

2.2 Patient Population

The population will consist of 750 infertile women with PCOS, age ≥18 to ≤40 years, diagnosed by the modified Rotterdam Criteria: subjects must have ovulatory dysfunction and either one of the remaining two criteria, hyperandrogenism (clinical or biochemical) or polycystic ovaries on ultrasound, with exclusion of secondary causes of PCOS. Additionally, the couple will have no other major infertility factor, and the subject will have at least one patent fallopian tube and a normal uterine cavity, and a partner with a sperm concentration of 14 million/mL in at least one ejaculate.

2.3 Study Design

This will be a multi-center, prospective, double-blind clinical trial of clomiphene citrate (CC) vs. letrozole for 5 cycles (or approximately up to 25 weeks). The randomization scheme will be coordinated through the central data coordination center (DCC) and the randomization will be stratified by each participating site. We have elected not to stratify by prior exposure to medication as this did not exert significant effects in our previous trial and would add an unnecessary layer of complexity to the randomization scheme.

2.4 Treatment

After progestin withdrawal, 750 women will be equally randomized to two different treatment arms: A) clomiphene citrate 50 mg every day for 5 days (day 3-7 of cycle), or B) letrozole 2.5 mg every day for 5 days (day 3-7 of cycle), for a total of 5 cycles or 25 weeks. Dose will be increased in subsequent cycles in both treatment groups for non-response or poor ovulatory response up to a maximum of 150 mg of clomiphene a day (x 5 days) or 7.5 mg of letrozole a day (x 5 days).

2.5 Primary Efficacy Parameter

Live birth will be the primary outcome, and the live birth rate will be the efficacy parameter.

2.6 Secondary Efficacy Parameters

Secondary efficacy parameters will include singleton live birth rate, abortion rate, time to pregnancy, ovulation rate, pregnancy complication rate, birth weight, neonatal complication rate, predictive factors for response including DNA polymorphisms, quality of life, and cost effectiveness.

2.7 Statistical Analysis

The primary analysis will use an intent-to-treat approach to examine differences in the live birth rate in the two treatment arms. Primary efficacy analysis will be done by comparing the treatment groups with respect to the primary outcome of live birth using the Pearson chi-square test. As secondary, supportive analysis, we will fit a logistic regression model to compare the treatment arms with respect to the primary outcome of live birth, adjusting for other factors such as randomization stratification of study site and prior exposure to study medications. The analysis of other secondary (supplemental) outcomes measured over time will entail the application of statistical methods that have been developed for correlated data since repeated observations will be made over time on each individual. For secondary outcomes such as hormone levels, a linear mixed-effects model will be fit where the main independent variables will be treatment group, time, and their interaction as well as the designed randomization stratification factors as covariates. Logistic regression models will be used in secondary analyses to evaluate the predictive value of treatment arm, clinical site, prior exposure to either clomiphene citrate or letrozole, body mass index, and other explanatory variables on binary outcomes (e.g., singleton live birth, abortion). Cox proportional hazards models and a Kaplan-Meier method will be applied to compare time to pregnancy in the treatment groups.

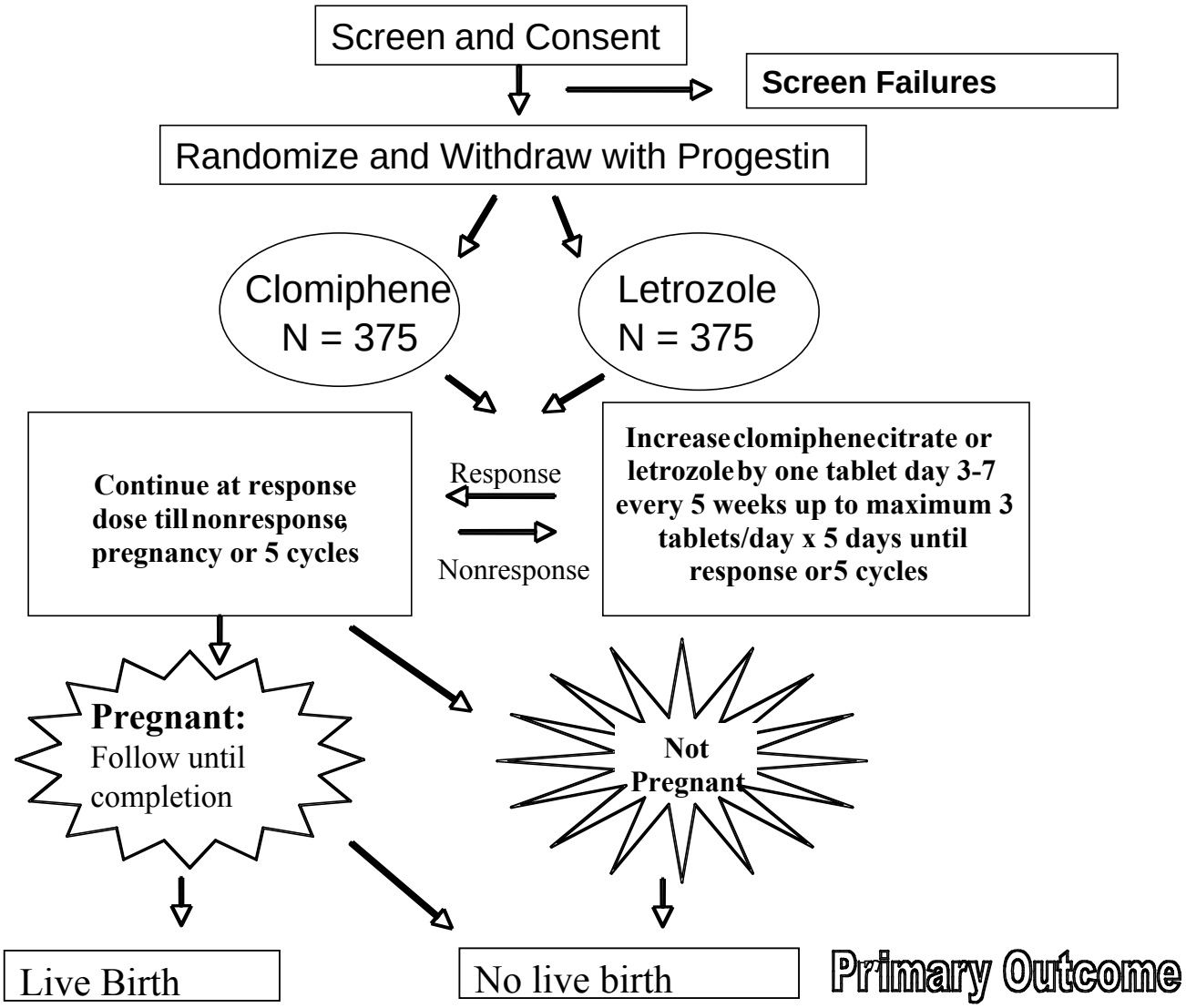
2.8 Anticipated Time to Completion

A total of 4 years will be required to complete the study after start up; 31 month enrollment period, 5 month treatment period, with 9 month additional observation to determine pregnancy outcomes. This will be accomplished by enrolling ~3.45 women with PCOS per center per month over the enrollment period (N = 7 RMN sites).

2.9 Regulatory Compliance

We have submitted an Investigational New Drug application to FDA (IND#: 101671; Serial #: 0002) and registered this trial on http://clinicaltrials.gov/show/NCT00719186 (NCT#: NCT00719186).

2.10 Study Diagram



3 Background and Significance

3.1 Overview

Polycystic ovary syndrome (PCOS) may be the most common cause of female infertility (Hull 1987). Anovulation (Hull 1987), increased early pregnancy loss (Homburg, Armar et al. 1988), and later pregnancy complications (Bjercke, Dale et al. 2002) all have been implicated in the poor fecundity of these women. The etiology of the syndrome is not fully understood (Ehrmann 2005) and controversy surrounds both the diagnostic criteria (2004) and the treatment of the disorder (Ehrmann 2005). There are insufficient adequately powered and designed clinical trials to guide the treatment of infertility in women with PCOS. Most of these trials have focused on surrogate outcomes such as circulating hormone levels or ovulation, and not the only meaningful outcome, i.e. live birth, that these women desire (Legro and Myers 2004; Johnson 2006). The best treatment for achieving a live birth is unknown, though for decades CC has been the front line therapy to treat the disorder as was upheld in the previous Pregnancy in Polycystic Ovary Syndrome (PPCOS) study conducted by the Reproductive Medicine Network (RMN) (Legro, Barnhart et al. 2007).

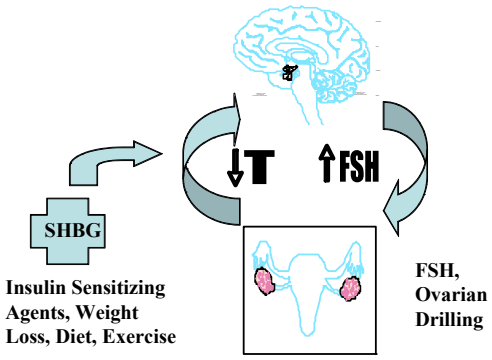


Figure 1. The shared mechanism of all commonly used ovulation induction treatments in PCOS may be by improving hyperandrogenism.

3.2 Pathogenesis of Subfecundity in PCOS

Women with PCOS display inappropriate gonadotropin (elevated luteinizing hormone (LH) secretion) and sex steroid production (elevated androgens and unopposed estrogen production), morphological changes in the ovary (polycystic), and oligo-ovulation (Stein and Leventhal 1935; Goldzieher and Axelrod 1963; Rebar, Judd et al. 1976). They also as a group, tend to display decreased insulin mediated glucose uptake (insulin resistance), with accompanying compensatory hyperinsulinemia (Dunaif, Segal et al. 1989). Targeting these abnormalities, alone or in combination, have all been noted to improve ovulation (Nestler, Jakubowicz et al. 1998; Azziz, Ehrmann et al. 2001 Apr) and fertility (Vandermolen, Ratts et al. 2001 Feb) in women with PCOS. (Lord, Flight et al. 2003 Oct 25). The previous RMN PPCOS trial, demonstrated that clomiphene citrate (CC) was superior to metformin in achieving a live birth, and that improvement in hyperandrogenism (HA) predicted response. These observations supported by another Dutch multicenter trial of CC and metformin (Moll E 2006) (no advantage of the combination on ovulation or live birth rate), suggest that improving insulin sensitivity *per se* may not be as critical as improving HA in restoring ovulation and achieving a live birth.

In fact, in examining all of the myriad commonly used therapies to induce ovulation in women with PCOS, it is noted *that all have been shown to improve HA, either directly or indirectly (whereas many have no effect on insulin sensitivity*) (Figure 1). Also interestingly in our preliminary models of predictive factors in live birth from the PPCOS trial, hirsutism was noted to have a dose response adverse effect on live birth (i.e. increasing hirsutism was associated with decreased fecundity), and was a more powerful predictor than circulating androgen measures which fell out of the larger model (Table 1). Hirsutism emerged as an important baseline predictive factor for live birth. The pilosebaceous unit has been noted to have excessive activity in hyperandrogenic states. It is possible that acne and sebum production may be better predictive markers, and they are more reliably assessed than hirsutism. Therefore we have included them in the current protocol.

Table 1. Predictive baseline factors for live birth from the PPCOS trial.

Effect	Odds of Live Birth
Clomiphene vs. Metformin	4.03 [2.13,7.61]
Combined vs. Metformin	5.16 [2.76,9.66]
Baseline BMI (kg/m^2)	
<30 vs. >34	1.79 [1.08,2.95]
30-34 vs. >34	1.29 [0.72,2.30]
F-G Hirsutism Score	
< 8 vs. ≥ 16	2.68 [1.49,4.80]
8-15 vs. ≥ 16	1.55 [0.92,2.60]

(unpublished data)

3.3 Risk/Benefit Assessment of Clomiphene Citrate in PCOS

The PPCOS trial further cemented the role of CC as front line infertility therapy for women with PCOS. There were also results to solidify the clinical experience that the use of CC also has drawbacks and there is a need for better ovulation induction agents (one not fulfilled by metformin). These include a relatively poor success rate (only 23% had a live birth in the CC group of the PPCOS trial and a further 25% never had a single documented ovulation during the study period), concern about multiple pregnancies (6% multiple pregnancy rate with one triplet gestation), and the possible adverse effects of estrogen antagonism on target organs, including potentially a thinner endometrium and decreased chance for embryo implantation, and concern about the long half live and effects of accumulated CC metabolites on ovulation and pregnancy, including the possibility for fetal teratogenic effects. A recent large case series of 911 babies found overall low malformation rates with either letrozole or CC (though major cardiac anomalies were more common with CC (1.8%) compared to the letrozole group (0.2%)(Tulandi, Martin et al. 2006). Many women also experience vasomotor symptoms, including hot flushes, headaches, and mood changes during treatment with CC that discourage its use.

3.4 Aromatase Inhibitors (AIs) as Ovulation Induction Agents

AIs, primarily letrozole, have been promoted as potent ovulation induction agents in the published literature (Holzer, Casper et al. 2006). These drugs were developed as adjunctive agents to treat breast cancer and they work as selective aromatase inhibitors, thus preventing the conversion of androgen to estrogen. The mechanism of action is not improvement in hyperandrogenism, but by releasing the hypothalamic pituitary axis from inappropriate and excessive estrogen feedback (which in PCOS results primarily from peripheral conversion of elevated circulating androgens). Third generation aromatase inhibitors can be given orally and are well tolerated (main side effects are GI disturbances, asthenia, hot flushes and back pain). Their half-life is around 45 h, significantly less than CC. They decrease circulating estrogen levels by nearly 100%, and also increase circulating androgen levels (as well as intra-ovarian levels). This would seem counter intuitive to the findings from the PPCOS study that HA is a primary treatment target in PCOS and would offer new insight into the pathophysiology and treatment of PCOS.

However, increases in sex hormone binding globulin (SHBG) with AIs may result in less peripheral hyperandrogenism, despite the increase in serum testosterone through aromatase inhibition. In the PPCOS study, metformin reduced total testosterone more than CC, but CC substantially increased SHBG more than metformin resulting in greater reduction in bioavailable peripheral (and potentially intrafollicular) levels of androgen. Studies have shown that AIs improve the endometrial thickness compared to CC and while multiple follicles are induced, this appears to be less likely with aromatase inhibitors (Atay, Cam et al. 2006; Bayar, Tanriverdi et al. 2006).

The risk benefit ratio of letrozole compared to anastrozole is uncertain. While there was some initial concern that letrozole may be associated with increased malformation rates based on an abstract presentation (not yet published in a peer review journal but criticized for small numbers and poor methodology) at the annual meeting of ASRM in Montreal in 2005 (Novartis of Canada sent doctors a letter advising them not to use letrozole for infertility- see Section 7.4.4 below for a copy of the letter), the published results of the fetal effects of letrozole have been reassuring. This issue is discussed further in the protocol in more detail. A recent large randomized trial from Egypt compared anastrozole (1mg) to letrozole (2.5 mg) in women with PCOS (N = 220) (Badawy, Mosbah et al. 2007). The study noted ovulation occurred in 183/295 cycles (62%) in the letrozole group and 177/279 cycles (63.4%) in the anastrozole group, whereas pregnancy occurred in 36/295 cycles (12.2%) in the letrozole group and 42/279 cycles (15.1%) in the anastrozole group and the differences were not statistically significant. The authors concluded that there was no difference in the miscarriage rate between anastrozole and letrozole when used for ovulation induction in women with CC-resistant PCOS. However, this group has published in the last year 3 separate randomized trials that have randomized a total of 828 subjects (Badawy, Abdel Aal et al. 2007; Badawy, Mitwally et al. 2007; Badawy, Mosbah et al. 2007). This would represent an unprecedented recruitment rate for a single academic center for a single disorder testing a single class of drugs (AIs) and raises doubts about the methodology of these trials. Nonetheless they are included in this discussion because they are the largest published trials to date.

Unfortunately as the above paragraph suggests, the quality of trials with aromatase inhibitors that have appeared to date is extremely poor. They have been limited by small numbers, lack of a placebo or reference treatment, inadequate blinding of study medication, focus on surrogate outcomes such as follicle number or endometrial thickness, and also by heterogeneity, including the inclusion of subjects with ovulatory disorders and unexplained infertility in the same trial (Mitwally and Casper 2001; Al-Omari, Sulaiman et al. 2004; Atay, Cam et al. 2006; Bayar, Tanriverdi et al. 2006; Elnashar, Fouad et al. 2006). Recently the investigative group in Egypt reported another large trial that randomized 438 women to either clomiphene or letrozole which found no significant differences in pregnancy rates between the two treatment groups (Badawy, Abdel Aal et al. 2007). While the authors claimed that this was a prospective randomized trial, there is no description of the randomization scheme and no mention of blinding of the medication, again raising doubts about the methodology of this investigative team. The pregnancy rates for the clomiphene group was also nearly twice that of the PPCOS study, which were likely due to differences in the patient population compared to a U.S. PCOS population. For example, the Egyptian population was substantially younger and thinner than the U.S. population. Thus, although the sample size represents the largest to date for a trial with an aromatase inhibitor, the overall quality of the trial and the translation to our population is poor. A more recent study from Bangladesh showed marked superiority of letrozole over clomiphene (Begum et al. 2008). Table 2 summarizes the pregnancy rates in women with PCOS who have taken letrozole. While there have been other studies performed with letrozole in women with unexplained infertility, we do not feel that these data are informative for women with primary anovulatory infertility due to PCOS.

Table 2. Conception rates with Letrozole alone and vs. Clomiphene Citrate (CC) in women with PCOS

Author	Type	Total Subjects	Failed CC	Durations	Conception Rate (Letrozole Group)	Conception Rate (CC group)
	Non-Randomized					
Mitwally et al, 2000	Open label letrozole only	N = 10 (PCOS)	Yes	One cycle	20% (2/10)	N/A
Mitwally et al, 2001	open label letrozole only	N = 12 (PCOS)	Yes	One cycle	25% (3/12)	N/A
Elnashar et al, 2006	Open label letrozole only	N = 44 (PCOS)	Yes	One cycle	13.6 % (6/44)	N/A
	Randomized					
Bayar et al, 2006	RCT letrozole vs. clomiphene	N = 46 (anovulatory infertility)	No	Multiple, mean = 2.6 cycles)	9% (5/52)	12% (9/67)
Atay et al 2006	RCT open label	N = 106 (PCOS)	No	Not stated	21.6% (11/51)	9% (5/55)
Badawy et al, 2007	RCT open label letrozole vs. clomiphene	N = 220 (PCOS)	No	Multiple mean = 2.3 cycles	37.6% (82/208)	43% (94/220)
Begum et al, 2008	RCT open label	N = 64 (PCOS)	Yes	Up to 6 cycles	40.3% (13/32)	19% (6/32)

There is only one dose ranging studies of letrozole in women with PCOS and it was underpowered to detect differences in pregnancy rates. The study was again conducted by Badawy et al from Egypt and they compared the three most commonly used doses of letrozole: 2.5, 5 and 7.5 mg (Badawy, Mitwally et al. 2007). A total of 179 patients were randomly recruited in this prospective study with 58, 61 and 60 patients in each dosage group respectively. This study reported a significantly higher ($P < 0.05$) number of follicles (total, > 14 mm and > or = 18 mm) on the day of administration of human chorionic gonadotropin in the 7.5 mg group, associated with significantly fewer ($P < 0.05$) days of stimulation. However the pregnancy and miscarriage rates were similar in the three groups. The adverse event profile at the higher dose remains unclear (including the increased potential for multiple pregnancy), and our study design will utilize an escalating dose scale to attempt to answer the important question or risk/benefit ratio of varying doses of letrozole in women with PCOS.

Letrozole is increasingly used to induce ovulation in women with polycystic ovary syndrome as a first line agent. The number of citations for the use of aromatase inhibitors to induce ovulation has risen steadily in the last 5 years. An ISI Web of Knowledge search on this topic revealed 71 articles published in this area, and a total of 748 citations to date since their first publication in 2001, 103 citations in the first four months of 2008 alone. Multiple editorials in prominent publications have recommended further study of these agents in properly designed trials (Casper 2007; Tulandi and DeCherney 2007).

NOTE: Merck-Serono has conducted several phase II dose ranging studies of anastrozole in women with PCOS, and contact between the NIH program staff and medical personnel at Merck-Serono was initiated about the possibility of using anastrozole instead of letrozole in this study. Due to the multiple hurdles and the possible conflicting nature of these trials, we have elected not to pursue further collaboration on this drug. Regardless of the outcome of the Merck-Serono Phase II trials with anastrozole, we believe that it is important to establish the efficacy of letrozole (if for instance the Phase II trials with anastrozole are negative) and proof of concept for AIs in ovulation induction with PCOS (if they are positive), and the dose escalation plan described in this protocol eliminates the need for a placebo, as we will use overencapsulated medications. Ultimately the protocol as described with letrozole may be in the best interests of the patient population the RMN is serving, as letrozole will soon be available in generic form which should substantially decrease its costs, whereas anastrozole was being studied with a dose not currently available on the world market.

3.5 Summary of Preliminary Data

We interpret the preliminary data as being promising for the use of letrozole to induce ovulation in women with PCOS. However, the true magnitude of the effect of letrozole is difficult to discern given the poor design of the trials (i.e. no blinding, inadequate methods of randomization, etc.), their failure to report birth outcomes, and the population bias of these trials. Therefore we have elected in our power analysis to choose for an absolute difference between regimens that we would like to detect. Further study of mechanisms of action of aromatase inhibitors, including effects on circulating sex steroids, gonadotropins, follicular development, endometrial quality and their effects on quality of life are needed, as well as studies of the pharmacoeconomics, all of which we intend to incorporate into this study.

4 Objectives

4.1 Primary Research Hypothesis

The primary research hypothesis is that ovulation induction with an aromatase inhibitor (letrozole) is more likely to result in live birth than ovulation induction with a selective estrogen receptor modulator (clomiphene citrate) in infertile women with PCOS. A safety hypothesis will also be incorporated into the primary research hypothesis in which we hypothesize both treatments are equally safe for mother and child.

4.1.1 Primary Outcome Measure

The primary outcome measure is the occurrence of a live birth during the study period. The primary analysis of live birth rate within the two treatment conditions will employ an intent-to-treat approach. Hence, patients will be analyzed according to the treatment group to which they are assigned, even if they did not receive the intended treatment or received only a portion of it. Safety measures will be the number and type of reported adverse events in subjects and offspring.

4.2 Secondary Research Hypotheses

1. Treatment with letrozole is more likely to result in singleton pregnancy compared to treatment with clomiphene citrate. Singleton pregnancy is defined as presence of a single intrauterine gestational sac with a single fetal pole and observable heart motion.
2. Treatment with letrozole will less likely result in a first trimester intrauterine fetal demise (IUFD) than treatment with clomiphene citrate. A first trimester IUFD is defined as a pregnancy that ends before 13 weeks gestation.
3. Treatment with letrozole is more likely to result in ovulation (increased ovulation rate) compared to treatment with clomiphene citrate. Ovulation is defined as a midluteal progesterone level $\geq$ 3 ng/mL.
4. The shortest time to pregnancy will be with letrozole.
5. Age, body mass index, SHBG, testosterone, LH, Anti-Mullerian Hormone (AMH), and degree of hirsutism and acne will be significant predictors of ovulation and conception regardless of treatment.
6. Improvement in SHBG, testosterone, AMH, and LH levels will be significant predictors of ovulation and conception regardless of treatment.
7. DNA polymorphisms in estrogen action genes will predict response to study drug.
8. Quality of Life will be better on letrozole than clomiphene.
9. Letrozole will be more cost effective at achieving singleton pregnancies than clomiphene.

4.3 Treatment Design, Study Summary and Study Population

4.3.1 Treatment Design

This will be a multicenter, prospective, double-blind trial of oral clomiphene citrate vs. letrozole in the treatment of infertility in patients with polycystic ovary syndrome. Patients will be randomized to receive either an initial dose of 50 mg of CC or 2.5 mg of letrozole for 5 days per menstrual cycle. They will be monitored at monthly intervals during the anticipated luteal phase for response to medication as measured by physical, ultrasound, and hormonal parameters.

The dose may be adjusted according to the response or maintained if adequate response is determined. The maximum dose of clomiphene citrate will not exceed 750 mg/cycle and the maximum dose of letrozole will not exceed 37.5 mg/cycle. The study will last for 5 cycles or approximately 25 weeks.

4.3.2 Study Summary

Recruitment Process: See description which follows.

Screening Visit: (Coordinator and physician)

1. Obtain signed informed consent
2. Comprehensive history and complete physical examination including vital signs, height, weight, hip and waist measurements, BMI, pelvic exam with Pap smear as necessary per current AGOG guidelines
3. Assessment of hirsutism by Ferriman Gallwey score and acne standard acne lesion counts, and facial sebum by sebumeter
4. Transvaginal ultrasound of the uterus and ovaries
5. Study Hormonal testing: Urine pregnancy test, serum pregnancy test and serum progesterone level in the local lab, serum to central core lab for Total testosterone (T), estradiol (E2), Progesterone (P4), follicle stimulating hormone (FSH), luteinizing hormone (LH), anti-mullerian hormone (AMH), sex hormone binding globulin (SHBG), etc.
6. Inclusion Laboratory testing at local lab (T/SHBG, FSH, TSH, 17-OH Progesterone, Prolactin) and Safety labs (CBC, Renal, and Liver Profile)
7. Begin completion of QOL surveys: FSFI, FSDS, SF-36, Prime MD PHQ, PCOS-QOL, FertiQol and Sleep Habits instruments for women. Males complete the IIEF, SF-36, Prime MD, FertiQol and Sleep Habits instruments.
8. Confirm Couple Inclusion Critera (no other infertility factors) with assessment of tubal patency and semen analysis.
9. Pre-conception counseling (including completion of Genetic Risk Factors Questionnaire), optional Rubella, Varicella (only if there is no history of chicken pox) and HIV screening, and folic acid prescription.
10. Dispense Progestin to induce withdrawal bleed, with instructions to begin medication once eligibility is determined.
11. Randomization: (No Visit necessary)

12. Randomization to treatment group once eligibility from screening visit is determined (prior to baseline visit).

Baseline Visit (Visit 2: Day 1-5 of the subsequent menstrual cycle with Day 1= first day of vaginal bleeding)

1. Weight, and vital signs
2. Urine pregnancy test
3. Serum pregnancy test
4. Transvaginal ultrasound exam
5. Hormonal blood draw (P4 to be run in local lab and serum for core lab)
6. Finish completion of all QOL surveys
7. Dispense home urine pregnancy tests.
8. Dispense study medication.
9. Orient and dispense intercourse and menstrual journal logs.
10. Blood sample (DNA) for pharmacogenomics study.
11. Blood sample for repository.

Monthly Midluteal Visit (Midluteal 3 weeks after initiation of study medication +/- 4 days up to 5 Visits):

1. Weight, blood pressure, sebumeter assessment
2. Query for adverse events, and concomitant medications
3. Collect and re-dispense menstrual and intercourse journal logs
4. Urine pregnancy test
5. Serum pregnancy test (Optional)
6. Transvaginal ultrasound exam
7. Hormonal Blood draw (P4 and quantitative hCG as necessary for local lab and serum for core lab)
8. Dispense home urine pregnancy test.
9. Collect and dispense study medication.

Monthly Menses Serum Pregnancy Test

1. Serum qualitative pregnancy test with menses or after 5 weeks amenorrhea prior to starting next cycle of ovulation induction.

Pregnancy Visits (only with conception):

1. Adverse Event query

2. Serum quantitative hCG levels
3. Transvaginal ultrasound as above, but with number of gestational sacs, location, dimensions, presence and size of fetal parts, and documentation of visualization of fetal heart motion, documentation of any pregnancy related abnormalities.

End of Treatment Visit (all subjects):

1. To take place after completion of the 5th cycle or after pregnancy, whichever comes first.
2. Complete physical examination to be performed, including vital signs, height, weight, hip and waist measurements as well as repeating hirsutism, acne, and sebum assessments
3. Urine pregnancy test
4. Serum pregnancy test (Optional)
5. Transvaginal ultrasound for subjects with a positive pregnancy test
6. Blood draw for progesterone level, hCG screen, and central core lab collection
7. Repeat Safety Labs
8. Repeat QOL surveys
9. Collect menstrual and intercourse journal logs
10. Query for adverse events and concomitant medications
11. Arrange follow up for subjects who have conceived and obtain release of records for pregnancy and neonatal records.

4.3.3 Study Population

750 women with PCOS actively seeking pregnancy (or 375 per each treatment arm) aged ≥18 to ≤40 years will be enrolled in the seven RMN sites and participating CREST scholar sites. The overall goal of the inclusion and exclusion criteria is to identify a population of healthy women with PCOS who have anovulation as the exclusive infertility factor. Anovulation will be obtained by history or anovulatory midluteal progesterone levels. In addition all subjects will have evidence of either hyperandrogenism or polycystic ovaries on ultrasound. Hyperandrogenism will be determined by evidence of hirsutism on exam or by biochemical elevations in total testosterone or free androgen index. Thus in addition to oligomenorrhea, the presence of any one of the following: hirsutism, an elevated total testosterone level, an elevated free androgen index, or a polycystic ovary will qualify for the diagnosis of PCOS. These biochemical laboratory cutoffs for androgens may vary according to assay methodology. Where existing medical records are used to verify inclusion or exclusion criteria, the site should keep a copy of these in the source documents. A general list of exclusionary medications requiring a washout period is found in the appendix. This list is not exhaustive, and questionable medications can be looked up to see if they belong to one of the families of exclusionary medications, or the Project Leader and DCC can be queried.

4.3.4 Inclusion Criteria

Key Inclusion Criteria (Must have ovulatory dysfunction and either hyperandrogenism **or** PCO)

1. Chronic anovulation or oligomenorrhea: defined as spontaneous intermenstrual periods of ≥45 days or a total of ≤8 menses per year, or for women with suspected anovulatory bleeding, a midluteal serum progesterone level < 3 ng/mL is indicative of chronic anovulation. For women who have been on ovarian suppressive therapy or other confounding medication (i.e. insulin sensitizing agents) within the last year prior to the study, a history of ≤8 menses per year prior to the initiation of this prior therapy will qualify as evidence of oligomenorrhea. For women with more regular bleeding patterns, but who are suspected to be experiencing anovulatory bleeding, a midluteal progesterone level < 3ng/mL will be evidence of ovulatory dysfunction and qualify as anovulation. Undiagnosed persistent vaginal bleeding should be diagnosed and treated prior to enrollment.

2. Hyperandrogenism (either Hirsutism or Hyperandrogenemia) or Polycystic Ovaries on Ultrasound:

a. Hirsutism is determined by a modified Ferriman-Gallwey Score >8 at screening exam (Hatch, Rosenfield et al. 1981 Aug 1). ***Subjects who have hirsutism do not need local or core labs documenting elevated androgen levels.***

b**.** Hyperandrogenemia can be determined from local labs. Local cutoffs will be pre-determined by each site prior to study initiation. Hyperandrogenemia will be defined as an elevated total testosterone, or free androgen index (FAI)(in our lab at Penn State College of Medicine a total T > 50 ng/dL or a free androgen index >5) will allow entry into the study (Legro, Driscoll et al. 1998). The FAI is calculated from measurable values for total T and SHBG, as previously described (Miller, Rosner et al. 2004), using the following equation: (FAI = Total testosterone in nmol/L / SHBG in nmol/L) X 100. Outside lab values obtained within the last year documenting elevated T or FAI levels are sufficient to meet criteria of hyperandrogenemia.

c. Polycystic Ovaries on Ultrasound: We will use the revised Rotterdam criteria for diagnosing polycystic ovaries (Balen, Laven et al. 2003). PCO will be defined as either an ovary that contains 12 or more follicles measuring 2-9 mm in diameter, or an increased ovarian volume (> 10 cm^3) on one ovary for entry into the study. If there is a follicle > 10 mm in diameter, the scan should be repeated at a time of ovarian quiescence in order to calculate volume and area if the subject does not otherwise qualify for the study. The presence of a single polycystic ovary (PCO), either by volume or morphology, is sufficient to provide the diagnosis.

4.3.5 Exclusion Criteria

We will exclude subjects with medical conditions that represent contraindications to CC, aromatase inhibitors and/or pregnancy or who are unable to comply with the study procedures. We will exclude subjects with poorly controlled Type I or Type II diabetes; undiagnosed liver disease or dysfunction (based on serum liver enzyme testing); renal disease or abnormal serum renal function; significant anemia; history of deep venous thrombosis, pulmonary embolus, or cerebrovascular accident; uncontrolled hypertension, known symptomatic heart disease; history of or suspected cervical carcinoma, endometrial carcinoma, or breast carcinoma; undiagnosed vaginal bleeding, and use of other medications known to affect reproductive function or

metabolism (e.g., OCP, GnRH agonists and antagonists, anti-androgens, gonadotropins, anti-obesity drugs, somatostatin, diazoxide, ACE inhibitors, and calcium channel blockers). As in PPCOS we will allow a 2 months washout period for subjects who desire to participate and discontinue exclusionary medications (most commonly OCP, but also possibly metformin), and a period of observation or treatment for correctable conditions.

4.3.6 Couple Inclusion Criteria

1. Sperm concentration of 14 million/mL in at least one ejaculate within the last year, with at least some motile sperm.
2. Ability to have regular intercourse during the ovulation induction phase of the study.
3. At least one patent tube and normal uterine cavity as determined by sonohysterogram, hysterosalpingogram, or hysteroscopy/laparoscopy within the last 3 years. An uncomplicated intrauterine non-IVF pregnancy and uncomplicated delivery and postpartum course resulting in live birth within the last three years will also serve as sufficient evidence of a patent tube and normal uterine cavity as long as the subject did not have, during the pregnancy or subsequently, risk factors for Asherman's syndrome or tubal disease or other disorder leading to an increased suspicion for intrauterine abnormality or tubal occlusion.
4. No previous sterilization procedures (vasectomy, tubal ligation) that have been reversed. The prior procedure may affect study outcomes.

4.3.7 Specific Exclusion Criteria

1. Current pregnancy.
2. Patients on oral contraceptives, depo progestins, or hormonal implants (including Implanon). A two month washout period will be required prior to screening for patients on these agents. Longer washouts may be necessary for certain depot contraceptive forms or implants, especially where the implants are still in place. A one-month washout will be required for patients on oral cyclic progestins.
3. Patients with hyperprolactinemia (defined as two prolactin levels at least one week apart > 30 ng/mL or as determined by local normative values). The goal of eliminating patients with documented hyperprolactinemia is to decrease the heterogeneity of the PCOS population. These patients may be candidates for ovulation induction with alternate regimens (dopamine agonists). A normal level within the last year or on treatment is adequate for entry.
4. Patients with known 21-hydroxylase deficiency or other enzyme deficiency leading to the phenotype of congenital adrenal hyperplasia. 21-hydroxylase deficiency will be excluded in all patients by a fasting 17-hydroxyprogesterone (17-OHP) level <2 ng/mL (Azziz, Hincapie et al. 1999 Nov). If relevant, this level should be determined in the follicular phase, because the 17-hydroxyprogesterone level is likely to be elevated beyond this range if the patient is in the luteal phase of an infrequent ovulatory cycle. In the case of elevated fasting 17-OHP levels in the follicular phase, an ACTH stimulation test will be performed. A 1-hour stimulated value > 10 ng/mL will be an exclusion (Moran, Knochenhauer et al. 1998). As 21-hydroxylase deficiency is a congenital

condition, any normal level in the past of 17-hydroxyprogesterone allows entry into this study.

5. Patients with menopausal levels of FSH (> 15 mIU/mL). A normal level within the last year is adequate for entry.
6. Patients with uncorrected thyroid disease (defined as TSH < 0.2 mIU/mL or >5.5 mIU/mL). A normal level within the last year is adequate for entry.
7. Patients diagnosed with Type I or Type II diabetes who are poorly controlled (defined as a glycohemoglobin level > 7.0%), or patients receiving antidiabetic medications such as insulin, thiazolidinediones, acarbose, or sulfonylureas likely to confound the effects of study medication; patients currently receiving metformin XR for a diagnosis of Type I or Type II diabetes or for PCOS are also specifically excluded.
8. Patients with liver disease defined as AST or ALT > 2 times normal or total bilirubin >2.5 mg/dL.
9. Patients with renal disease defined as BUN > 30 mg/dL or serum creatinine> 1.4 mg/dL.
10. Patients with significant anemia (Hemoglobin < 10 g/dL).
11. Patients with a history of deep venous thrombosis, pulmonary embolus, or cerebrovascular accident.
12. Patients with known heart disease that is likely to be exacerbated by pregnancy.
13. Patients with a history of, or suspected cervical carcinoma, endometrial carcinoma, or breast carcinoma. ACOG guidelines for cervical cancer screening should be followed.
14. Patients with a current history of alcohol abuse. Alcohol abuse is defined as > 14 drinks/week or binge drinking.
15. Patients enrolled simultaneously into other investigative studies that require medications, proscribe the study medications, limit intercourse, or otherwise prevent compliance with the protocol. Patients who anticipate taking longer than a one month break during the protocol should not be enrolled.
16. Patients taking other medications known to affect reproductive function or metabolism. These medications include oral contraceptives, GnRH agonists and antagonists, antiandrogens, gonadotropins, anti-obesity drugs, anti-diabeteic drugs such as metformin and thiazolidinediones, somatostatin, diazoxide, ACE inhibitors, and calcium channel blockers. The washout period on all these medications will be two months and a list is found in the appendix.
17. Patients with a suspected adrenal or ovarian tumor secreting androgens.
18. Patients with suspected Cushing's syndrome.
19. Couples with previous sterilization procedures (vasectomy, tubal ligation) which have been reversed. The prior procedure may affect study outcomes, and patients with both a reversed sterilization procedure and PCOS are rare enough that exclusion should not adversely affect recruitment.

20. Subjects who have undergone a bariatric surgery procedure in the recent past (<12 months) and are in a period of acute weight loss or have been advised against pregnancy by their bariatric surgeon.
21. Patients with untreated poorly controlled hypertension defined as a systolic blood pressure ≥ 160 mm Hg or a diastolic ≥ 100 mm Hg obtained on two measures obtained at least 60 minutes apart.

5 Study Design

5.1 Type of Design

This will be a multi-center, prospective, double-blind clinical trial of clomiphene citrate (CC) vs. letrozole with 750 infertile women with PCOS that will last for approximately 25 weeks. The randomization scheme will be coordinated through the DCC and the randomization will be stratified by each participating site.

5.2 Rationale for Design

Aromatase inhibitors have been theorized to improve outcomes when used for anovulatory infertility compared to clomiphene citrate, including lower multiple follicular recruitment, lower multiple pregnancy rates, and higher pregnancy rates potentially due to more favorable endometrial development with associated improved implantation. A double blind trial is needed to test these hypotheses and to establish the safety and efficacy of aromatase inhibitors compared to the current gold standard, i.e. clomiphene citrate to induce ovulation in women with PCOS. In order to do this in a double-blind manner, CC and letrozole will need to be overencapsulated. The RMN has used this approach previously (in the PPCOS study). It is anticipated that other studies undertaken by the RMN will also use CC that will result in cost savings to the network.

5.3 Recruitment/Informed Consent Process

Based on the average PPCOS accrual rate of 2.6 randomized subjects per RMN site per month (the overall recruitment rate of PPCOS was 2.9 randomized subjects/month, but 90% were randomized at RMN sites and 10% at SCCPIR sites) and assuming a 33% higher yield of screened subjects based on the broader diagnostic criteria of this study protocol (the primary reason for PPCOS study exclusion was inadequate serum T levels (McGovern, Legro et al. 2007)), (i.e. 3.46 subjects/RMN site/month), and assuming just the 7 RMN sites in this trial (i.e. 24.2 randomized subjects per month), we anticipate a recruitment period of 31 months, which could be significantly shortened with the addition of other sites (SCCPIR) or more efficient recruiting by the new RMN sites. Our current plan is to begin this protocol only at the RMN sites and to see if we meet recruitment goals, with the fall back plan to add SCCPIR sites if needed. Again the prior experience with the initial PPCOS trial will significantly streamline the start up and recruitment period of this trial. The recruitment strategy will be multifocal and will be followed after the identification of willing research subjects by the informed consent process. The recruitment strategy for the study is described below and will rely on a combination of local and national strategies.

5.4 Recruitment

5.4.1 Hospital/Local Health Care Referrals

Each PI will recruit subjects from his individual practice as well as faculty/resident continuity clinic. If a potential research subject is recruited by the PI from his own private practice, this participant will be enrolled and consented by a study coordinator or another co-investigator involved in the study. The care of this participant will be followed by someone other than the PI throughout the study period. A principal investigator may not enroll, consent, or treat his own patient if she is involved in this research. Ongoing contact with practice and faculty members as well as with residents will be made by the PI and nurse coordinators, reminding them of the

inclusion criteria, importance of the study, etc. In addition, the PI will make contact with other departments in the hospital, i.e. family practice, pediatrics, adolescent medicine, medical endocrinology, who also see and treat these patients and talk about ovulation induction in PCOS. Contacts with local physicians will be made and/or grand rounds will be given to disseminate information about the study and ovulation induction in PCOS.

5.4.2 Local Publicity Office

PIs should meet with their local Public Relations official and plan a news release about the study. They should be available for any newspaper, radio, or TV stories that result from this. The full gamut of local media sources should be utilized. Often there is greater yield with more extensive coverage in smaller local outlets, than brief mentions in outlets with larger circulation. News releases should mention the uniqueness of a study with pregnancy as an outcome and the benefits of improving care of women, as well as the development of new methods for fertility treatment.

5.4.3 Local Advertisements

Local advertisements can consist of unpaid flyers that are posted and paid advertisements. Flyers should be posted in the medical center and local clinics or other public places where these are allowed. Advertisements will be placed on local radio stations or local newspapers on a regular basis, and money for this has been budgeted. Suggested copy should advertise for "Are you infertile with 8 or fewer menstrual periods a year…" and not PCOS per se. All responses to paid advertisements (# of contacts, # screened, # randomized) should be tallied. This will allow us to determine the cost effectiveness of these advertisements and their role in enhancing diversity in our study. These strategies should be reviewed and data reviewed from individual sites to guide the budgeting of future funds towards the most cost effective strategy, which may vary from site to site.

5.4.4 Local PCOS/Infertility Support Groups

There are a number of national PCOS patient support groups including Polycystic Ovarian Syndrome Association, Inc (PCOSA) and PCO Support that have a large network of affiliated local support groups, as do the nationwide infertility support groups, such as Resolve or the American Infertility Association (AIA). Contact should be made with leaders of the national support groups as well as local support groups to spread information about the study. Site investigators and nursing personnel should volunteer to participate in local meetings of patient support groups to dispense information about the study.

5.4.5 National Professional Organizations

Contact should be made with the publicity offices of the Endocrine Society, The American Society for Reproductive Medicine, the Society for Reproductive Endocrinology and Infertility, the Society for Gynecologic Investigation, and the American College of Obstetricians and Gynecologists to issue press releases and mention/support the study in mailings/newsletters, web sites, etc.

5.4.6 National Support Groups

PIs should offer to attend/speak at National Support group annual meetings about the study. The American Infertility Association (AIA) also holds an annual meeting typically in the New York City area. Ads for the study should also be placed in newsletters of these organizations.

5.4.7 Web Sites

The study will be prominently displayed on the RMN web site. Additionally each RMN/SCCPIR center should have a web page devoted to this study with information and contact information and information should be available at the NICHD web site with links to each RMN center. Links to the NICHD site should be requested at the major PCOS/infertility web sites. An ad should also be placed at "Center Watch" on the web. The trial will be registered at NIH.gov and as many clinical trial registries as possible to increase detection of our trial. Other creative uses of the internet, such as posting the study and advertising for subjects on "Craigslist.org" should be attempted.

5.5 Informed Consent

Subjects who are interested will first be screened by an intake to verify that they meet basic inclusion criteria (i.e. age, oligomenorrhea, partner availability, etc.). Those who qualify will be scheduled for a screening visit. Subjects will be mailed a study packet with a copy of the informed consent document and other relevant study materials for them to review prior to the visit. Upon presentation to the RMN site, the study will be explained in detail and all questions answered prior to signing written informed consent to participate in the study. The male partner will also be required to sign a Male Consent Form at the time of the screening visit. It is important to obtain his consent for participation in the study due to the requirements of intercourse and semen analysis inclusion criteria and the information collected on the Quality of Life surveys. This consent process for the male partner may occur on site or off site, via a telephone consenting process per each individual site IRB requirement. As per NICHD Clinical Research Policy guidelines, the principal investigator at the RMN site should not be the primary caregiver for study participants.

5.6 Screening Visit

The goal of screening will be to establish a diagnosis of PCOS, to exclude major medical illnesses, and to verify that there are no other significant infertility factors in the couple. Costs of this infertility evaluation will not be covered by the study, as these tests are routinely performed as part of a diagnostic evaluation before proceeding with ovulation induction.

However in order to provide access to underrepresented groups in medical studies, an evaluation may be provided by sites to subjects without infertility insurance benefits. These tests may all be performed in one day or in the case of the couple inclusion criteria over several days. All tests relating to data that will likely be part of the baseline data or final analyses, (i.e. physical exam, serum for the core lab, ultrasound, and QOL surveys) should be obtained on a single day. However, QOL surveys may be spread between the Screening and Baseline visit. Local inclusion labs or safety labs may be obtained at an earlier (for instance T, SHBG, FSH, Prolactin) or at a later visit (i.e. safety labs) if that results in time or financial savings to the site.

5.7 Physical Exam

A physical exam with a standard pelvic and breast exam will be performed on all patients by a study physician. Height, weight and waist and hip circumferences will be recorded to the nearest 0.1 cm, 0.1 kg and 1 cm, respectively. Waist will be measured at the level of the umbilicus and hip circumference will be measured at the widest diameter. Participants will be weighed while dressed in light clothing, without shoes. Weight will be collected at each individual visit, however height, waist and hip circumferences are only collected at the screening and termination

visits. Blood pressure will be determined in the right arm in the sitting position. Large cuff will be used as necessary. Blood pressure will be assessed at each visit. Elevated blood pressures (≥160/100) will be repeated following acclimation to the study environment. All patients who are 21 or older should have had a normal Pap smear as recommended by current ACOG guidelines. If not, one should be performed at the baseline exam. Patients with cytological abnormalities will need to have these resolved prior to study entry. A hirsutism assessment will be made via the modified Ferriman-Gallwey hirsutism score (Figure 2) by trained study personnel (Hatch, Rosenfield et al. 1981 Aug 1). An acne assessment will be made by trained personnel using a standard acne lesion assessment (count) diagram and definitions (Table 3). Photographic examples of each grade will be provided to investigators as well as training to study personnel. When counting facial acne lesions, it is important that all lesions be counted, both non-inflammatory and inflammatory, examining areas of the forehead, cheeks, and chin and avoiding the nose. Additionally we will measure facial sebum with a sebumeter (Leyden, Shalita et al. 2005; Thiboutot, Shalita et al. 2005; Leyden, Thiboutot et al. 2006; Pariser, Thiboutot et al. 2006; Thiboutot, Pariser et al. 2006; Thiboutot, Shalita et al. 2006). Androgens can also cause increased sebum production and abnormal keratinization in the pilosebaceous unit, contributing to the development of acne (Chen, Thiboutot and Zouboulis 2002). Patients with complete inactivation of the androgen receptor in type I androgen resistance syndrome do not develop hirsutism and acne (Hargreave 2000; Rosenfield, 2005). Acne and sebum levels may, in addition to hirsutism be a significant prognostic factor for success in the trial.

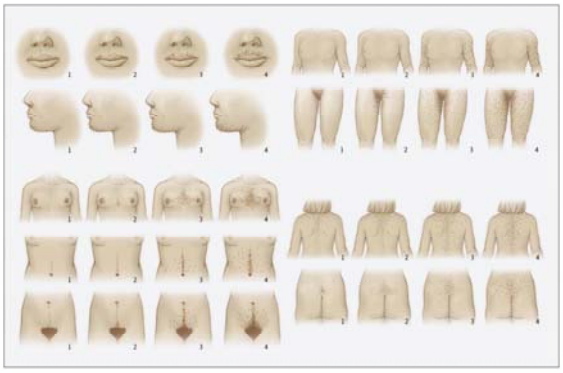


Figure 2. Modified Ferriman-Gallwey Hirsutism Scale

Table 3. Acne Lesion Definitions

Name	Description
Open Comedone (Blackhead)	Results when residual skin oil, makeup, dirt, dead skin, and small hairs impact a sebaceous follicle and prevent the pore from functioning correctly. If the pore is open, the comedone will be dark in appearance, and is called a blackhead.
Closed Comedone (Whitehead)	Non-inflammatory comedone with a white center.
Papule	An inflammatory comedone that resembles a small red bump on the skin.
Pustule	An active infection of the skin that consists of dead skin cells and bacteria. These lesions are spherical in appearance and are filled with pus. Often reddish in color, pustules may be painful and will break open easily if scratched or bumped.

Nodule	A natural progression of a papule. They appear very similar to papules, but are inflamed and penetrate deep into the skin. They are often very painful.

5.8 Transvaginal Ultrasound Exam

An ultrasound exam will be performed with a transvaginal probe. The following measures will be obtained: uterine dimensions, leiomyoma presence and size, other uterine abnormalities, endometrial thickness, ovarian size in three dimensions, the size of the largest ovarian follicle, antral follicle count (all follicles <10 mm diameter on ultrasound exam), and ovarian morphology. Ovarian size is determined by measuring the largest plane of the ovary in two dimensions and then turning the vaginal probe 90 degrees and obtaining a third measurement. Endometrial thickness is the largest anterior-posterior measurement of the endometrium in the sagittal plane. Ovarian volume is determined by the formula for a prolate ellipsoid (length x width x height x $\pi/6$)(Pache, Hop et al. 1991). Polycystic ovary volume is determined by the revised Rotterdam criteria of Balen et al (Balen, Laven et al. 2003), which is defined as at least one ovary having a volume greater than 10 cm^3 with no cysts or follicles greater than 10 mm mean diameter. Polycystic ovary morphology will de determined by a follicle count > 12 in a single plane (Balen, Laven et al. 2003). If the patient has had no prior test of tubal patency, this may be the desired time to perform a sonohysterogram to determine tubal patency.

5.9 Laboratory Exam

Women will present fasting for 12 hours at the initial screening visit. Blood work will be sent as described above in the inclusion and exclusion criteria to identify appropriate study subjects. This blood work is found in Table 4 below and will be run in the local lab. In the presence of hirsutism, it will not be necessary to confirm biochemical androgen excess through local lab assays, however for those subjects without overt hirsutism, it may be prudent to confirm biochemical androgen excess before completing the remainder of the laboratory evaluation (in local labs). Women who deviate from the recommended cutoffs for laboratory screens will proceed with further evaluation as necessary (e.g. repeat prolactin or perform ACTH stimulation test for elevated fasting 17- hydroxyprogesterone) or be excluded from further study. Costs of these blood tests that determine if the anovulation is consistent with PCOS will be covered by the study. An aliquot of serum from this visit and each subsequent monthly fasting visit will be frozen and maintained for core lab determinations (serum from two 7.5 cc red top tubes at baseline and from each subsequent monthly fasting visit). 1 ml of serum from these visits will be aliquoted into 1.5 cc microfuge tubes and will be stored at -20^o to -70^o C and batched for periodic shipping to the central core lab facility for eventual assay. The purpose of aliquoting is to preserve basal levels of potential analytes in a frozen state until assay to avoid the deleterious effects of thawing and re-freezing.

Table 4. Screening labs of PCOS women (run in local labs)

PCOS Diagnostic Labs (if no hirsutism)	PCOS Inclusion/ Exclusion labs	PCOS Safety Screen
1. Testosterone OR 2. SHBG and calculated Free androgen index	1. Prolactin 2. TSH 3. 17-OHP 4. FSH 5. Progesterone 6. Glucose	1. Liver Profile ALT/AST Total Bilirubin 2. CBC 3. Renal Profile BUN/Creatinine

	7. Pregnancy	4. Pap smear (if no recent results available) 5. Transvaginal U/S

The determination of eligibility can presumably be made in one visit. Other sites may prefer to perform this in a stepwise fashion over two or more visits (first verify screening labs to allow eligibility such as T or SHBG and then check diagnostic infertility tests). It is anticipated that the eligibility visits can be completed in less than four weeks.

5.9.1 Central Core Laboratory

Screening labs to determine eligibility will be run in the local RMN site labs. Given the variability of assays between labs, secondary analyses of baseline predictive factors and response variables will be performed in a central lab at the Ligand Assay Core lab at the University of Virginia. Glucose, insulin, serum androgens (Total T, Androstenedione, DHEAS, as well as estradiol, progesterone SHBG, etc.), will be measured at the Ligand Assay Core according to established assays.

We have successfully used this lab, with excellent quality and low pricing due to NICHD support in the PPCOS study (Legro, Myers et al. 2006; Legro, Barnhart et al. 2007). We coordinated shipment of samples (both baseline and monthly visits) from the RMN sites to this lab without difficulty. These assays all have <10% interassay coefficients of variation (http://www.healthsystem.virginia.edu/internet/crr/ligand.cfm). We have obtained approval to use this facility from the head of the Reproductive Sciences Branch at NICHD, Dr. Lou DePaolo. We will also measure AMH (Jonard, Pigny et al. 2005; Pigny, Jonard et al. 2006) and other assays as needed (for instance Inhibin A and B) at this core facility, which offers a wide variety of custom and fixed assays. Samples are labeled with a unique patient identifier, type of the visit and date of the visit. Samples are likely to be shipped to the Core lab on a quarterly basis (unless mutually agreed otherwise by the Core lab and RMN).

5.9.2 DNA Core Facility

We will obtain blood for DNA at the baseline visit, since all subjects will undergo a thorough and consistent phenotyping process. We have had long term experience in this process (through the NIH sponsored U54 SCCPIR studies on the genetics of PCOS at Penn State and U Penn and through the PPCOS trial). In the first PPCOS trial the collection of specimens was instituted as an addendum long after the study had begun (and thus half of the completed subjects and dropouts were lost to follow up). Therefore, this will be a part of the initial protocol, though subjects will have the option to opt out of this segment of the study or limit the use of their specimen on the consent form. Blood (in EDTA tubes, labeled with a unique patient identifier and the date of draw) will be sent to a core facility on a regular basis (every 2 weeks) where DNA will be extracted and stored for the future analyses. DNA will be extracted as reported (Urbanek, Legro et al. 1999 Jul 20). Our primary purpose in obtaining DNA is to explore genetic markers that predict response via pharmacogenomic studies. Our secondary aim is to serve as repository to participate in genome wide association studies. In both cases there will be no release of personal identifiers and we will obtain a Certificate of Confidentiality as we did in prior studies. In the previous RMN study we successfully identified a novel SNP in a metformin response gene STK11 (Legro, Barnhart et al. 2007). Examples of genes to be tested are found in the table below:

Table 5. Proposed SNP and microsatellite markers

GENE	MARKER ID	ALLELES	MAF [1]	MAF [2]	LOCATION
ESR1	rs2234693	C/T	C: 0.41	C: 0.44	Intron: IVS-401/*Pvu*II 14)
CYP2C9	rs1934963	C/T	C: 0.15	C: 0.16	Intron
CYP2C9	rs1799853	C/T	T: 0.10	T: 0.10	Cys144Arg
CYP2D6	rs3892097	C/T	T: 0.18	T: 0.16	Acceptor Splice Site: 1846G>A

[1] Minor Allele Frequency (MAF) was taken from dbSNP (http://www.ncbi.nlm.nih.gov/SNP).
[2] MAF estimated.

We propose to ship blood on a regular basis to a core lab for DNA extraction and storage to pursue pharmacogenomic protocols upon the completion of the trial. We will genotype subjects for a variety of candidate genes, including estrogen response genes such as the estrogen receptor and P450 metabolizing enzymes using high-multiplex single-nucleotide polymorphism (SNP) genotyping on an Illumina platform as was done with the PPCOS Study. This resource may also prove useful for genome wide association studies or other studies of the genetics of PCOS, oligomenorrhea, and hyperandrogenism.

5.9.3 Serum Bank

We will establish a serum bank at baseline prior to randomization. This serum bank will serve a twofold purpose. One is that this can serve as a repository to run additional serum assays for novel markers of PCOS or treatment success that are discovered while the study is ongoing. Second, it will serve as a source of samples for further studies including proteomics, metabolomics, etc.

Baseline serum samples (5cc) and DNA, (in the form of two 4.5 cc vials of frozen whole blood, one 15 cc centrifuge tube of frozen blood clots and blood spots on FTA cards) will be collected for storage and eventual DNA extraction at the baseline visit. We anticipate that the clinical sites will collect the serum, separate into 5 to 10 1cc aliquots in cryovials, labeled with study ID, sample type, the date of draw and a unique identifier (in the form of a freezer safe barcode label). The remaining blood clots from the serum collection tubes will then be transferred into one similarly labeled 15 cc centrifuge tube and frozen. The whole blood will also be collected by the sites, and frozen in 2 labeled 4.5cc cryotubes. The FTA collection cards, with 4 125µl dried blood spots, will be stored at the sites at 4^{o} C in sealed plastic bags with a desiccant. The serum, blood clots and whole blood will be stored at -20^{o} C or -80^{o} C at the clinical sites until they are transferred to the repository site, along with the FTA blood spot cards, likely on a yearly basis.

Once the vendor for the repository has been selected, a detailed repository protocol will be submitted for ethics approval at each clinical site. This protocol would cover the establishment of the repository, the shipment of the samples off site, the potential uses for the biological materials, and confidentiality safeguards. As such, no samples collected during the course of this study

would be removed from the clinical site until the repository location has been established and individual site IRB approvals have been obtained. When shipping the samples to the repository, they will be couriered on dry ice from the clinical sites to the repository site at infrequent intervals, at most, quarterly, but as infrequently as yearly. The proposed repository will have alarmed and monitored storage, with appropriate back-up -80^{o} C freezer capacity in the event of freezer failure. Alternate uninterruptible power supplies will also be a requirement to prevent catastrophic sample loss. A computerized inventory system with a back-up system is also required, as well as a way for the DCC to get immediate access the inventory data, preferably on line. The repository site must conform to HIPAA, the NCI statement on best practices for biospecimen resources and to the International Society for Biological and Environmental Repositories (ISBR) best practices for repositories 2008. Additionally, the repository should conform to the NIH statement "NIH Policy Framework on Legal and Ethical Issues Associated with Human Specimen and Data Collections" which is in the final stages of approval. Storage of these samples at the repository will be a minimum of 5 years, and perhaps further into the future. We would expect that DNA extraction of the whole blood would be performed at the repository, in a batch fashion, once the study has been closed.

Subjects will be able to opt in or opt out of these studies, analogous to the DNA studies proposed above via separate signature on the consent form. We will also store leftover serum samples for additional post hoc studies. Study subjects will be separately consented to store and use their leftover serum samples from the study and will similarly be able to opt out.

5.10 Quality of Life Measures (QOL)

Mood, quality of life, and sexual function will be assessed at baseline and at the end of the study visit. Quality of life will be assessed by the Medical Outcomes Survey (Prime MD-PHQ), and Short Form 36 (SF-36) (Ware JE 1993). Female sexual function will be assessed by the Female Sexual Function Inventory (FSFI) along with the Female Sexual Distress Scale (FSDS) (Rosen, Brown et al. 2000). This measure is considered the "gold standard" paper and pencil assessments of sexual function and has excellent psychometric properties (Rosen, Brown et al. 2000). The International Index of Erectile Function (IIEF) is a multidimensional scale for assessment of erectile dysfunction. The measure addresses the relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) (Rosen et al, 1997). We will assess quality of life relating to infertility with the FertiQol survey. We will also obtain a validated PCOS Quality of Life (QOL) questionnaire (Cronin, Guyatt et al. 1998; Guyatt, Weaver et al. 2004). Abnormal Sleep patterns (including sleep apnea) have been associated with insulin resistance, systemic inflammation, and increased cardiovascular risk in women with PCOS (Vgontzas et al 2001, Tasali E et al 2008). There may also be some impact on fertility and we will investigate this in our study. The Sleep Habits questionnaire, which was the standard measure used to collect data for the 10-year long multi-center NHLBI Sleep Heart Health Study, will be administered. (Kump, Whalen et al, 1994)

5.11 Exclusion of Other Infertility Factors

As is routine standard of care in many infertility practices, other infertility factors that would require additional evaluation or alternate therapies will be excluded prior to randomization in the study. These factors include male factor and tubal factor. It is estimated that, if necessary in the case of a couple with no prior testing, the screening evaluation could be completed in one visit, if there has been no prior evaluation. This would consist of the patient bringing in a semen specimen from the partner, obtaining baseline history, physical, and blood tests, and performing

an ultrasound with sonohysterogram or hysterosalpingogram on the subject to determine tubal patency. An uncomplicated intrauterine non-IVF pregnancy and uncomplicated delivery and postpartum course resulting in live birth within the last three years will also serve as sufficient evidence of a patent tube and normal uterine cavity as long as the subject did not have, during the pregnancy or subsequently, risk factors for Asherman's syndrome or tubal disease or other disorder leading to an increased suspicion for intrauterine abnormality or tubal occlusion.

Sonohysterogram is a procedure where fluid (usually sterile saline) can be infused through an intrauterine catheter that contains a balloon to occlude the cervical canal, such that the contours of the uterine cavity can be examined, and free fluid can be seen accumulating in the posterior cul de sac indicating at least one fallopian tube is patent.

Hysterosalpingogram is a similar procedure however, this procedure is performed under radiography using a radioactive contrast dye that is injected and visualized flowing through the fallopian tube.

Sonohysterogram has been found to have a sensitivity approaching hysterosalpingography for detecting uterine anomalies and tubal patency (around 70-80%) (Fleischer, Vasquez et al. 1997 Jun; Darwish and Youssef 1999). It was used successfully in the previous PPCOS study. Sonohysterography is chosen for this study because of its lower cost compared with hysterosalpingography. However, if it is judged by the principal investigator to be clinically preferable based on the standard clinical practice at each site, the principal investigator may deem it necessary to perform the hysterosalpingogram or other test of tubal patency such as a laparoscopy, if needed, and these results will be accepted. These studies will be performed by staff at each site proficient in the use of this technique.

If a patient (or her partner in case of the semen analysis) has had any test in the last year that is normal or within normal range for the reference lab, this may be accepted in lieu of repeating the test for screening. This applies to all inclusion/exclusion criteria except labs that qualify as safety labs (See Safety Screens under Table 4). In the case of a test for tubal patency, the results will be accepted if performed within the previous three years. This protocol acknowledges that there will be site to site variation in terms of the insurance coverage of the diagnostic infertility procedures. A sonohysterogram is an office-based procedure that utilizes existing ultrasonography technology. Andrology labs exist at every study site and a semen analysis is a low cost procedure. In order to enhance access to the study for women from a variety of backgrounds, some sites may elect to cover the costs of these tests out of RMN funds. Consent forms should explicitly state what tests will be covered by the study, and which will be the responsibility of the patient.

5.12 Preconception Counseling

During the baseline evaluation all patients will be provided with preconception counseling. At a minimum this will consist of offering to verify rubella immune status, offering to check Varicella status if there is no history of chicken pox, and offering HIV screening and referral for treatment as necessary. In addition, all patients will be given a prescription for prenatal vitamins containing a minimum of 400 micrograms of folate as recommended by the U.S. Public Health Service. Giving a prescription for folic acid alone is also acceptable. Subjects are to take this pill daily during the study and also during a pregnancy. Sites may provide the prenatal vitamins or folate to patients without pharmacy benefits.

The PPCOS study demonstrated that increasing baseline BMI is a significant negative predictor for live birth as well as associated with a variety of adverse pregnancy outcomes and complications. Therefore, all subjects who are obese (BMI > 30) will be counseled about the potential benefits of weight loss prior to conception and recommended to pursue this as a first line therapy (although there are no adequate studies to document that this improves outcomes in this population or any obese population). However, because anti-obesity therapy, whether it be lifestyle or pharmacologic is frequently unsuccessful, obesity *per se* will not be an exclusion criteria. Bariatric surgery for morbidly obese women with PCOS remains a treatment option, but because the role of bariatric surgery in improving reproductive outcomes is uncertain and because these procedures involve substantial risk and cost to study subjects, this will not be incorporated into the study protocol.

Similarly smokers will also be counseled about adverse effects and advised to stop smoking, though continued smoking will not be an exclusionary item.

All patients will fill out a genetic risk factor questionnaire (See the Appendix for copy of the questionnaire) for genetic disease and if indicated, further counseling about genetic risks will be coordinated by the PI at each site. Patients who are rubella non-immune will be offered the rubella vaccine, and their entry into the study delayed for 1 month as per CDC recommendations. The site may cover this cost for patients without insurance benefits.

5.12.1 Screen Failures

Many screen failures may qualify for rescreening after correction of modifiable conditions (such as wash out of exclusionary medications) or re-testing of borderline laboratory cutoffs (i.e. prolactin levels). It is anticipated that patients who may fail screening due to a medically treatable condition, such as hypothyroidism, hypertension, or mild iron deficiency anemia, may eventually become eligible for re-screening, assuming that other inclusion/ exclusion criteria have not changed (e.g. oligo-amenorrhea as an inclusion criteria, or elevated prolactin levels as an exclusion criteria). These cases will be handled on an individual basis after consultation with the Protocol Leader and the DCC.

5.13 Counseling about Menstrual and Intercourse Diaries

All subjects will receive counseling and journal logs to track menstrual bleeding and intercourse during the study.

5.13.1 Timing and Tracking of Intercourse Instructions

All subjects (and couples where the male partner is present) will be instructed to have intercourse on a regular basis during the study period. The male partner, if not present, will be informed of this recommendation when informed consent for participation in the study is obtained. The optimal frequency will be every 2-3 days. Subjects will be counseled that multiple episodes of intercourse within a short period (i.e. <24 h) can lead to diminishing returns in terms of sperm count and function, and therefore they should not "batch" their intercourse. The monthly visit will include a query about dates of intercourse and review of the intercourse diary. The importance of regular intercourse should be mentioned if the frequency on any week is < 2 episodes/week. An inquiry regarding possible causes should result when intercourse has occurred <2 times per week for two consecutive visits. Referrals should be made to appropriate caregivers if there is evidence of sexual dysfunction.

5.14 Adjuvant Therapy

Adjuvant therapy with other ovulation induction agents (GnRH agonists and antagonists, gonadotropins), or triggering ovulation with hCG, or performing intrauterine or intracervical inseminations will not be allowed for study subjects in this protocol.

5.14.1 Progestin Withdrawal

All patients, except those with evidence of a luteal phase progesterone level on baseline screening, will undergo withdrawal bleeding with progestin at the start of the study, at the discretion of the local PI. The patient will be given a supply of progestin at the baseline visit, (medroxyprogesterone acetate 5mg x 10 days), and progestin therapy can be instituted immediately after the screening visit, once eligibility criteria have been verified.

The PI may elect to give another comparable form of oral progestin to institute a withdrawal bleed. It will be up to the site to decide if the medication will be a charge to the subject or if the medication will be provided by the study at no cost.

5.15 Ancillary Studies at Baseline

It is possible that several sites may want to perform additional studies at baseline to further characterize the PCOS phenotype, such as more detailed studies of insulin action or body composition. These will be treated according to the RMN policy for ancillary studies.

5.16 Randomization/Treatment Initiation

Seven hundred fifty (750) women will be randomized to one of the two treatment conditions. Using a 1:1 treatment ratio, there will be 375 women assigned to each treatment group. The scheme will be a stratified randomization with permuted blocking (the block size is randomly permuted among 2, 4, and 6) within each stratum. The only stratification variable will be by site. Almac statisticians will generate the randomization scheme for the study. Because this is a double-blind study, the randomization scheme (including block size) will be disclosed to the DCC data manager, and not to any RMN investigators or staff, including the Protocol Lead Investigator. Unless otherwise specified, treatment group data will be presented in a blinded fashion within DSMB reports.

The site investigator will be provided a password protected account for WebEZ, which is a web-based secured randomization service. After the patient has signed an informed consent and all required baseline evaluation procedures have been completed, an Investigator or designee will login to WebEZ in order to randomize a patient into the trial. It is anticipated this will occur in the ~14 days between the screening visit and the onset of the withdrawal bleed after the subject has taken progestin.

The WebEZ will query the site for patient eligibility information. If the patient is eligible, the site will be provided with a patient identifier and a study kit number. The Study Coordinator at each site will be responsible for storing, dispensing, and performing pill counts on the study medication.

In the event that emergency unblinding is needed, only the site PI will be able to unblind a patient to treatment by calling the WebEZ emergency unblinding number. The site PI and DCC staff will receive notification from the central randomization service when emergency unblinding has occurred. With the exception of emergency unblinding, patients will not be unblinded until study findings are released.

5.17 Study Specific Procedures/Visits

An overview of the study visits is found in Figure 3 below. After screening and baseline visits, a monthly cycle will consist of two visits, one involved and the second just a blood test. The main visit will be a monthly midluteal visit that will involve questions, a brief exam, ultrasound, and blood work, and the second visit will be a menses visit at the time of menses or if menses are missed to obtain a serum pregnancy screen prior to starting the new dose of medication. This latter visit may be performed off site to ease patient participation in the study.

Figure 3. Flow Chart of Study Visits

	Screening Visit	Baseline Visit (Day 3)	Monthly Visit Cycle 1	Menses Visit 1	Monthly Visit Cycle 2	Menses Visit 2	Monthly Visit Cycle 3	Menses Visit 3	Monthly Visit Cycle 4	Menses Visit 4	Monthly Visit Cycle 5	Menses Visit 5 and End of Treat-ment Visit
Visit #	1	2	3	4	5	6	7	8	9	10	11	12
History	■	■	■		■		■		■		■	■
Full Exam	■											■
Brief Exam	■	■	■		■		■		■		■	■
Serum Pregnancy Screen	■	■		■		■		■		■		■
Safety/ Eligibility Labs	■											■
Fasting Phlebotomy for Study Parameters	■	■	■		■		■		■		■	
TV U/S	■	■	■		■		■		■		■	
QOL Measures	■											■
Blood for DNA		■										
Blood for Repository		■										

Physical Exam (Full & Brief): Height, weight, hip and waist circumference, blood pressure, facial sebum measurement, urine pregnancy test, local serum progesterone level, medication dispensing and accounting, query for adverse events and concomitant medications, collection and review of intercourse diaries and menstrual diaries.

Fasting Phlebotomy = Serum for the Central Core Laboratory

Transvaginal ultrasound will include endometrial thickness, ovarian volume, antral follicle count and size of ovarian cysts or developing follicles

QOL Measures = FSFI, FSDS, SF-36, Prime MD-PHQ, FertiQol, Sleep Habits and PCOS-QOL questionnaires

Visit 1 Screening Visit: A description of the screening visit in detail is found above under 2. Assessment for Eligibility. The results of the inclusion and exclusion labs which are run locally should be available within days. If the subject is eligible to participate, she will be instructed by telephone or email to take the progestin if needed (i.e. anovulatory serum progesterone level). If ineligible the subject will discard the progestin and will not participate further in the study. The screening visit will have no fixed timing in relation to last menses or day of the week, but will be scheduled at the discretion of the study subject and investigative team. Randomization will take place as soon as the eligibility requirements are met, although study drug will not be dispensed until the next visit (baseline visit).

Visit 2 Baseline Visit: The baseline visit will occur on Day 1-5 of the subject's cycle that either has occurred spontaneously (because the patient ovulated at the screening visit), or because she has experienced a withdrawal bleed after progestin challenge. Day 1 is defined as the first day of vaginal bleeding (spotting does not count). The subject will call in to the study coordinator with onset of her menses to schedule the baseline visit, which will take place within 5 days of the onset of normal menstrual flow.

If the subject does not have a menstrual bleed, either after progestin or spontaneous ovulation, she will be scheduled for this visit 2 weeks after the initiation of progestin or documentation of ovulation. These subjects will be managed on a case by case basis by the site PI depending on if they are pregnant and the results of the baseline ultrasound.

The Site PI may elect to re-challenge the subject who is not pregnant with oral progestin or proceed directly to the use of study medication without a withdrawal bleed. At the baseline visit, the subject will undergo the brief exam, the transvaginal ultrasound exam, and the fasting phlebotomy as described above in the eligibility visit and in the table of study visits. If the patient has consented for her blood to be drawn for the study DNA and the repository, that blood collection will also take place at this time. At this visit, the study subject will receive her first kit of study medication. A study drug kit will contain 3 bottles of 5 pills each of either Clomiphene Citrate (50mg) or Letrozole (2.5mg). The subject will be instructed to not start the medication until she has received a call from the study coordinator regarding the result of the serum pregnancy test. If the test is negative, she will be instructed to begin her study medication. The subject will be instructed when to start this, preferably by Day 5 of her cycle. At this time the subjects will be dispensed home pregnancy tests to be used throughout the cycle if pregnancy is suspected, and their journal logs to record menstrual flow, drug administration, intercourse frequency and adverse events throughout the study.

Monthly Midluteal Visits on Study Drug: The monthly visit will take place in the anticipated luteal phase of the cycle, and initially will be scheduled 3 weeks after the initiation of medication, with a window of 4 days on either side of this day (i.e. Day 17-25, assuming a Day 3 medication start, or Day 19-27, assuming a Day 5 start). At the monthly visit, the subject will undergo the brief exam, the transvaginal ultrasound exam, and the fasting phlebotomy (for serum for the core lab) as described above in the eligibility visit and in the table of study visits. The brief exam at this visit and all subsequent visits will consist of weight, blood pressure, facial sebum measurement, urine pregnancy test, local serum progesterone level, medication dispensing and accounting, query for adverse events and concomitant medications, collection and review of journal logs. A serum pregnancy test may also be performed if the PI thinks it is necessary. The

measures obtained from this visit that will help in the further management of the subject include a urine pregnancy test, a serum sample to the local lab to determine serum progesterone level, and the results of the ultrasound (including the endometrial thickness and echogenicity, as well as the number, size, and echogenic characteristics of follicles/cysts on the ovary (including an antral follicle count). Further management will be dependent on whether the subject has responded or not responded to the study medication based on the serum progesterone level.

There will be three possible scenarios at this visit: 1) the patient has an ovulatory progesterone level and will follow up for the monthly menses visit; 2) the patient has a progesterone level in the anovulatory range, and there is evidence of follicular development (i.e. a simple follicle with a mean diameter ≥ 12 mm is present on ultrasound), in which case a follow up visit to check a serum progesterone should be arranged within 2 weeks or a progesterone added to the monthly menses visit; or 3) the patient has a progesterone level in the anovulatory range and no evidence of follicular development, in which case the patient should be given either Progestin to induce a withdrawal bleed or study drug (at the next highest dose if applicable). In the presence of an ovulatory progesterone level at the midluteal ultrasound, the size and number of corpora lutea should not be over-interpreted, if the patient is without symptoms.

Monthly Menses Visit: The purpose of this visit is to prevent exposure of a fetus to study drug during the critical early period of implantation and organogenesis. The monthly menses visit will be obtained at the time of menses (spontaneous after ovulation) or within 2 weeks after the midluteal visit in the case of no menses (after ovulation). In the case of a patient who had an ovulatory progesterone level at the midluteal visit, this visit will consist of a serum pregnancy screen to verify the subject's pregnancy status. In the case of progestin challenge, either with or without menses, the subject will have both a serum pregnancy screen AND a serum progesterone level. If the serum pregnancy test indicates pregnancy or the progesterone level is in the ovulatory range, then the subject should not take study drug. This visit (consisting of serum pregnancy screen and possibly a progesterone level) may be performed at an outside lab and the results faxed to the study investigator if that eases the burden of study participation for the study subject. The end of study visit may be performed at the menses visit at the end of the 5th cycle for subjects who do not conceive during the study.

5.17.1 Responders

Responders will be identified on the basis of an elevated progesterone level consistent with ovulation (Progesterone > 3 ng/mL). An elevated level > 3 ng/mL is evidence of response (Guermandi, Vegetti et al. 2001 Jan). The rationale for this is that it may not be possible to determine a midluteal peak progesterone level, but that the study visit may overlap the peak, and be elevated, but not reach peak levels. While ultrasound may provide presumptive evidence of ovulation, serum levels of progesterone should guide further management.

5.17.2 Indeterminate Response

As noted above, the investigator will schedule a follow-up visit or phlebotomy based on the results of the ultrasound if there is evidence of follicular development, (i.e. a follicle with a mean diameter ≥ 12 mm), but the serum progesterone level is low or non-detectable. Such a finding may indicate that the subject is experiencing a longer than anticipated follicular phase but adequate follicular development. Subjects will be informed by telephone or email of the serum

progesterone levels and their meaning, and the subsequent plan. After the menses visit with a documented serum pregnancy test, the patient will again take the study drug from Day 3-7 of the cycle. Subjects may start study medication up to day 5 of the cycle with appropriate adjustment of the midluteal visit. Responders will continue at the same response dose until pregnancy, or a total of five cycles (or approximately 25 weeks) is reached.

5.17.3 Non-Responders

Non-response will be defined as the lack of an elevated progesterone level at the midluteal or subsequent follow-up visit if one has been scheduled, or based on the clinical impression of the site PI. A subject who has not ovulated and does not have evidence of follicular development will, as noted above, either receive progestin or the next dose of study medication.

If the patient fails to respond to treatment after these visits, she will be instructed to increase her study drug by one tablet per day for five days. The start of the increased dose will be designated as Day 3 of her cycle if she has not experienced a withdrawal bleed. Withdrawal with progestin is not necessary, but if it is utilized by the site PI, instructions are found in the following section. This dose will continue at this level if adequate ovulatory response is achieved until the completion of a total of five treatment cycles or approximately 25 weeks is reached. The dose may be increased by the end of the second cycle to the maximum dose if further nonresponse is noted. This may involve more than one cycle with the maximum CC or letrozole dose, as there are a total of 5 cycles in the study. However study subjects will never take more than 3 tablets per day or 15 tablets total/per cycle of study drug.

5.17.4 Induction of Withdrawal Bleeds for Non-Responders

There will be no mandatory induction of withdrawal bleeds for non-responders during the course of the protocol, unless as dictated by the PI at the site. The benefits and/or risks of this for short amounts of time (i.e. ≤5 months as in this protocol) have not been well described in the literature and as in the initial PPCOS trial we have opted to dispense with mandatory interval progestin use. The use and indication for inducing a withdrawal bleed should be noted on the case report forms. During the induction of the withdrawal bleed with medroxyprogesterone acetate (5 mg x 10 days) or other comparable progestin, the patient will not re-initiate study drug until instructed by the site PI upon experiencing a withdrawal bleed and obtaining a negative serum pregnancy test and a negative serum progesterone test (Progesterone < 3 ng/ml). If there is no spontaneous withdrawal bleed after the use of medroxyprogesterone acetate, a negative serum pregnancy test and a negative serum progesterone test will be a precondition to further use of study drug.

5.17.5 Dispensing of Study Drug after the First Cycle

At the midluteal visit each subject will be dispensed the next cycle of study drug in a study drug medication kit. Within that kit there will be 3 bottles of study medication. The study coordinator will instruct the subject to not take any medication until the progesterone and serum pregnancy results are back and reviewed with the subject. If anovulation is suspected, the study coordinator will instruct the subject to increase to the next dose of study medication (i.e. additional bottle of 5 study pills). No subject will receive more than the maximum dose for one cycle (i.e. three bottles of study medication or a maximum of 15 pills). It is anticipated that each study site will store and dispense the medication in this trial.

5.17.6 Breaks in Study Protocol

There may be breaks in the protocol for both anticipated and unanticipated reasons, but the breaks should not exceed 4 weeks, allowing the subject approximately 25 weeks to complete the protocol. Subjects should be counseled that they should be seeking conception for the full potential 25-week period. If personal or professional commitments will result in more than a four-week break from the protocol, subjects should not be enrolled. A break or breaks, up to four weeks, is allowable to facilitate timing of intercourse if there are other commitments or to allow recovery from a persistent ovarian cyst. Urinary pregnancy tests can be dispensed to check weekly for pregnancy during these breaks. Longer break(s) may be an indication for dismissing the patient from the protocol as non-compliant and should be cleared with the Protocol Leader and DCC.

5.17.7 Pregnancy Visits

A urine pregnancy test will be done at each visit, if the PI chooses, except for the menses visit. In addition, a serum pregnancy test will be done as well if the PI chooses, or if necessary. The subject will receive urinary pregnancy tests to use at home. She is to use one at the onset of bleeding after this visit (to confirm that it is not pregnancy related) or if she goes 2 weeks without menses after this visit where there has been confirmed ovulation, as this is likely to portend pregnancy. Alternatively, a blood test can be scheduled at the study site. Pregnancy will be confirmed, if suspected, by measurement of serum hCG. Pregnancies will be followed by the serial rise of serum hCG and when a threshold level is obtained (2,000-4,000 mIU/mL), ultrasound will be utilized to determine location of the pregnancy and number of implantation sites.

Patients who conceive will be followed through the study until the pregnancy has advanced to the point of determining the number of gestational sacs, their location, and fetal viability as determined by visualization of fetal heart motion by ultrasonography. At this point, at approximately 6-8 weeks gestational age, women will be referred to their prior or referring practitioner, or to an appropriate health care provider for prenatal care.

5.17.8 End of Treatment Visit

An end of treatment visit will be performed at the end of the ovulation induction phase for women who do not conceive in the trial, or with pregnancy if women conceive. The end of treatment visit should be performed as early in pregnancy as possible. A brief exam with the addition of a repeat of acne and sebumeter assessment and hirsutism will be collected. Subjects will return remaining study drug, their journal logs, and a final assessment of adverse events and concomitant medications will be done. Baseline measures will be repeated in all subjects, including safety labs and QOL surveys, (FertiQol will not be repeated in pregnant women). A final collection of blood for the core lab will also be collected. For any women with a positive pregnancy test, an obstetrical ultrasound will be done to determine viability at 6 to 8 weeks. For those women who have an ongoing pregnancy, arrangements will be made to follow the outcome of the pregnancy at the end of first trimester and also after delivery or termination of gestation. All pregnancies (including multiples) will be followed to determine the abortion rate, complication rates, and to determine pregnancy outcomes. Patients will be informed to notify study personnel of the outcome of the pregnancy and we will obtain release of record forms from treating physicians to obtain copies of relevant medical records. Phone contacts will be initiated if the patient has not contacted study personnel by six weeks beyond the original estimated date

of confinement. Delivery records will be requested to determine the birth weight, length of gestation, and any perinatal complication of mother or neonatal complication of the infant.

This methodology proved very successful in PPCOS for tracking pregnancy outcomes, and we will expand it in this study by obtaining more information about the neonatal course of the infant. At this visit we will also obtain separate consent to follow infants after birth to determine neurodevelopmental and behavioral outcomes as discussed in section 5.17.9.

5.17.9 Establishment of a Pregnancy Registry

As per the recommended guidelines by the FDA (http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133332.pdf) we intend to establish a pregnancy registry for this trial to establish outcomes of pregnancy. This will be a separate protocol and we will consent women who conceive individually to participate in this protocol. We will track the outcomes of all randomized subjects who have a positive serum pregnancy screen during the course of this study. We will record biochemical pregnancies (defined as positive serum pregnancy screens without ultrasonically detected pregnancies), ectopic pregnancies, and all intrauterine pregnancy losses both before and after 20 weeks including missed abortions, spontaneous abortions, elective abortions, fetal demises, and stillbirths. We will review pregnancy and birth records of the mother and of the fetus to establish neonatal morbidity and mortality and the presence of fetal anomalies. The infant will be examined at each site within 60 days of birth by a dysmorphologist for potential congenital anomalies. Fetal anomalies will be classified using the CDC birth defects code list (http://www.cdc.gov/ncbddd/bd/documents/MACDPcode%200807.pdf). We will extract from these records concomitant medical and obstetrical conditions, exposure information on all other medical products used, including prescription products, over-the-counter (OTC) products, dietary supplements, vaccines, and insertable or implantable medical devices. We will file individual case reports for all congenital anomalies, which will be considered a serious adverse event. Additionally we will provide to the FDA a written annual status report of the pregnancy registry as specified in the guidelines above. As per our discussions with the FDA, we acknowledge that our study will have minimum power to detect congenital anomalies given the relatively low number of pregnancies; however, it is viewed as an important first step. We also intend at a minimum to perform an annual parent directed screening questionnaire to assess the infant's developmental milestones for the first three years after birth as recommended by the FDA and to review the child's CDC growth curves and medical records.

6 Data Analysis

6.1 Justification of Effect Size

6.1.1 Prior Studies

The primary outcome is live birth, defined as delivery of any viable infant. There are good data about the per cycle cumulative live birth rate with clomiphene from the PPCOS data (Table 6). Unfortunately there are no comparative quality data from randomized trials of letrozole, given their poor designs and relative small sample sizes as summarized in the background section. The overall live birth proportion for subjects randomized to receive CC was 0.23 for the six month trial (0.20 for 5 months). We propose, based on our experience in PPCOS, to shorten the trial from 6 months to 5 months. There are several reasons for this. First, the live birth rate appeared to drop in the final 2 cycles of the PPCOS trial (Table 6). Second, we experienced greater dropout over time in the PPCOS trial (exceeding 10% in all treatment arms which threatened the external validity of the trial) and by shortening the current trial we will decrease the absolute number of dropouts. Third, it will result in a reduction in the cost of the trial while providing the same quality of scientific data. Lastly, it will allow a total of 3 attempts at the highest dose of clomiphene/letrozole analogous to clinical practice. The problem with dropout in the PPCOS trial appeared to be related to failure to respond (i.e. higher in the metformin group with a lower ovulatory rate), and it increased in all groups over time likely due to failure to ovulate and/or to conceive.

Table 6. Per Cycle Ovulation and Live Birth Results in Clomiphene arm of the PPCOS study

	Ovulations/ subjects	Live Birth/ ovulations
Visit 1	90/209 (43.1%)	10/90 (11.1%)
Visit 2	90/181 (49.7%)	10/90 (11.1%)
Visit 3	86/159 (54.1%)	9/86 (10.5%)
Visit 4	70/141 (49.6%)	10/70 ((14.2%)
Visit 5	58/119 (48.7%)	2/58 (3.4%)
Visit 6	55/99 (55.6%)	6/55 (10.9%)

6.1.2 Minimum Clinically Important Difference

The PPCOS trial was powered to detect a 15% absolute difference in pregnancy rates. Thus a benchmark of 15% difference between treatment groups was set as an important minimum of clinically important difference. We will be more conservative here and choose a 10% difference as clinically meaningful. We therefore hypothesize that letrozole will increase the live birth proportion by an absolute difference of 0.10 (i.e., a live birth proportion of 0.30).

6.1.3 Significance Testing

All primary statistical analyses will invoke the intent-to-treat paradigm where all randomized subjects are included according to their treatment assignment regardless of actual treatment received, protocol violations, etc.

Primary efficacy analysis will be done by comparing the treatment groups with respect to the primary outcome of live birth using the Pearson chi-square test.

As secondary, supportive analysis, we will fit a logistic regression model to compare the treatment arms with respect to the primary outcome of live birth, adjusting for other factors such as randomization stratification of study site and prior exposure to study medications.

The data will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, and quantiles) and frequency statistics (frequencies and percentages) for categorical variables. All hypothesis tests will be two-sided and all analyses will be performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC) or S-Plus software, version 7.0 (Insightful Corp., Seattle, WA).

6.1.4 Sample Size Calculations

A sample size of 300 subjects in each arm of the randomization yields 81% statistical power to prospectively demonstrate a 0.10 absolute difference in live birth proportions between treatment arms (0.20 for CC and 0.30 for letrozole) using the Pearson's chi-square test having a two-sided significance level of 0.05. The sample size has been inflated to 375/arm to allow for a dropout rate of 20%. The dropout rate in the CC arm of the PPCOS trial was 26.3%; however, that was a 6-month trial and involved weekly visits for progesterone levels, as ultrasound was not utilized. The monthly visits will be more user-friendly and also will avoid the weekly disincentive of a negative progesterone level in poor responders as we discovered in the PPCOS design. We anticipate therefore a lower drop out rate in this trial.

We recognize that the magnitude and the direction of the effect of letrozole remains something of an educated guess and we provide in Table 7 varying scenarios for decreased and/or increased live birth proportions for letrozole and the accompanying power based on it.

Table 7. Power based on varying Letrozole Live Birth Proportions

PPCOS Clomiphene Live Birth Proportion	Letrozole Live Birth Proportion	N per Group (0% Dropout)	N per Group (20% Dropout)	Power (%)
0.20	0.05	300	375	100.0
0.20	0.10	300	375	93.1
0.20	0.15	300	375	36.4
0.20	0.25	300	375	31.1
0.20	0.30	300	375	80.9
0.20	0.35	300	375	98.6

6.2 Secondary Analyses

6.2.1 Descriptive Summary

We propose a number of secondary analyses, including analyzing differences in ovulation, spontaneous abortion and multiple pregnancy rates, as well as developing baseline and treatment related predictive models for response (incorporating DNA markers), and finally to perform a cost effectiveness analysis.

6.2.2 Exploratory Analyses

We acknowledge that the power of our study for identifying differences in spontaneous abortion and multiple pregnancy rates is low due to the overall low numbers of these events (Table 8). However we performed power estimates for the secondary outcomes of multiple births and spontaneous abortion using a 2-sided Fisher's exact test with a significance level of 0.05. A Fisher's exact test was used because the proportions are so small for these secondary outcomes. Assumptions: (a) pregnancy rates are 26.7% clomiphene and 35.3% letrozole, (b) multiple birth rates are 6% clomiphene and 1% letrozole, and (c) spontaneous abortion rates are 25% clomiphene and 15% letrozole. Based on these assumptions, the proportions reported in the table below are obtained as follows:

6.2.3 Multiple Pregnancy

Clomiphene multiple birth proportion

= clomiphene pregnancy rate × clomiphene multiple birth rate

= 0.267 × 0.06 = 0.016

Letrozole multiple birth proportion

= letrozole pregnancy rate × letrozole multiple birth rate

= 0.353 × 0.01 = 0.004.

6.2.4 Spontaneous Abortion

Clomiphene spontaneous abortion proportion

= clomiphene pregnancy rate × clomiphene spontaneous abortion rate

= 0.267 × 0.25 = 0.067

Letrozole spontaneous abortion proportion

= letrozole pregnancy rate × letrozole spontaneous abortion rate

= 0.353 × 0.15 = 0.053

Table 8. Power Estimates for Secondary Outcomes based on the above Assumptions

Outcome	Clomiphene Proportion	Letrozole Proportion	N per Group (0% Dropout)	N per Group (20% Dropout)	Power (%)
Multiple Birth	0.016	0.004	300	375	19.4
Spontaneous Abortion	0.067	0.053	300	375	8.5

The analysis of other secondary outcomes will entail the application of statistical methods that have been developed for correlated data since repeated observations will be made over time on each individual, and these methods allow for both within-group and between-group comparisons to be assessed. For secondary outcomes such as hormone levels, a linear mixed-effects model will be fit where the main independent variables will be treatment group, time, and their interaction as well as the designed randomization stratification factors as covariates (Laird and

Ware 1982). The linear mixed-effects model is an extension of linear regression that accounts for the within-subject variability inherent in longitudinal trials and has the flexibility to adjust for potentially confounding covariates if deemed necessary. Potential covariates in the models include recruitment site, prior exposure to study medication, the baseline value of the outcome, and age. The effect size will be quantified from the mixed-effects models using the difference in the means between the treatment groups with their associated 95% confidence intervals (CI). Secondary modifiable continuous outcomes related to the improvement in the PCOS reproductive phenotype, such as changes in AMH or SHBG, will be analyzed similarly. For binary outcomes measured over time, generalized estimating equations with a logit link, an extension of logistic regression that accounts for correlated data, will be fit where the main independent variables will be treatment group, cycle, and their interaction as well as the designed randomization stratification factors as covariates (Zeger, Liang et al. 1988).

A Poisson regression model will be fit to the count of the number of ovulations to compare the arms with an offset being the logarithm of the number of cycle inductions completed per subject (Koch GG 1986). If overdispersion is an issue with the Poisson regression model, the overdispersion parameter will be estimated using the deviance divided by the degrees of freedom. The effect size from the model will be quantified using a rate ratio (RR) and corresponding 95% CI. The secondary outcomes of conception and pregnancy rates will be analyzed similarly.

Logistic regression models will be used in secondary (supplemental) analyses to evaluate the predictive value of treatment arm, clinical site, prior exposure to either clomiphene citrate or letrozole, body mass index, and other explanatory variables on binary outcomes (e.g., live birth, singleton live birth, abortion). Cox proportional hazards models and a Kaplan-Meier method will be applied to compare time to pregnancy in the treatment groups. Furthermore, candidate genes may influence the response to one or both treatments in a two-arm clinical trial. Our group has a long standing interest in this problem; we will examine susceptibility scores based on residuals from a regression equation modeling treatment success or failure as a function of key covariates and the treatment arm. Coefficients represent candidate genotypes and possibly interactions of these genotypes with other covariates in the model. The susceptibility residual values help to identify which members of the group had responses that were not adequately predicted and thus point the way to possible genetic influences.

6.2.5 Missing Data and Multiple Testing

Every attempt will be made to determine the full set of outcome values for each participant. Regardless of this effort, we expect there will be some missing data due to dropouts and missed visits. Most analytic methods are robust to small amounts of missing data and, where possible, we will consider analytic methods that assume the data are missing at random (MAR), often referred to as ignorable missingness. If the number of cases with missing data should exceed 10%, we will explore approaches that allow for non-ignorable missingness. These methods included selection models and pattern-mixture models (Little 2002).

Our primary analysis will test a defined primary hypothesis, and hence multiple testing is not an issue for the primary hypothesis testing. However, we will consider it when we conduct secondary data analyses. While the issue of p-value adjustment for multiple testing has long been a topic of statistical debate, it generally is accepted that p-values should not be the sole criterion for assessing significance of relations. Conclusions will be based on the preponderance of scientific evidence related to each hypothesis, considering point estimates and confidence

intervals, as well as statistical significance. Nonetheless, findings with marginal statistical significance (p-values in the range 0.01 to 0.05) will be interpreted cautiously, taking into consideration for multiple testing.

6.2.6 Adverse Event Analysis

Adverse events will be categorized and percentage of patients experiencing adverse events and serious adverse events during the treatment period will be detailed. Chi-square tests will be performed to examine differences in the proportion of total and categories of adverse events within each treatment arm. For each DSMB report, a list and summary of the reported adverse events will be presented in a blinded fashion, unless otherwise formally requested.

6.2.7 Interim Analysis

We propose not to do an interim analysis. We had planned to perform an interim analysis in the initial PPCOS trial, but the majority of subjects had been randomized by the time we had accumulated enough outcome data to perform the interim analysis, and it was skipped.

We anticipate a similar scenario in this trial.

The final data analysis will be completed after all live births in the trial. Unblinding of individual study subjects will not take place until all subjects have delivered and reported outcomes to the DCC.

7 Technical Aspects

7.1 Study Agent Preparation, Storage and Accountability

We propose to purchase study medication from generic manufacturers or low cost providers, and overencapsulate it to create a double-blind study. Because we will be giving the drugs in similar fashion, i.e. during 5 days of the early follicular phase, and will be adjusting the dose in a similar fashion, i.e. up to a maximum of three tablets a day, we propose to provide only a single drug kit with overencapsulated treatment agent to the patient. Thus we will skip the manufacture or purchase of identical placebo, as was necessary in PPCOS, as metformin was taken daily, whereas CC was only taken for 5 days per cycle. Because we are buying a generic agent for CC and potentially for letrozole, the name and dose is unlikely to be imprinted on the pill further aiding medication blinding.

Clomiphene citrate 50-mg tablets will again be purchased by Teva Pharmaceuticals. This dose will also allow for individual titration. The generic formulation of clomiphene citrate manufactured by Teva Pharmaceuticals has a shelf life of two years. Letrozole, with a brand name of Femara, is manufactured by Novartis and the exclusivity patent on this medication expired on 10/27/07. No current generic manufacturers have yet been identified, and it is deemed unlikely that Novartis will provide study medication given their concern about fetal effects expressed in the letter above and the expiration of their exclusivity patent. Currently we plan to purchase the brand name medication from a discount supplier, unless another source from a generic manufacturer becomes available in the near future.

The PPCOS trial had a delayed start up due to the FDA requirement that we perform stability testing on the clomiphene citrate provided by Teva Pharmaceuticals, as the manufacturer refused to provide this information. This also resulted in substantial cost to the RMN ($123,000) and this CC testing is presumably still valid. One advantage in using brand Femara is that this information is likely already on file at the FDA and accessible, whereas a generic maker may not provide us with that information, necessitating testing of this compound.

Significant cost was also added to the PPCOS trial by the fact that the two study drugs were packaged in two separate methods: bottle for the daily metformin XR and blister pack for CC. We propose to skip the more expensive blister packaging and utilize bottle preparations of a five day supply of study drug (each bottle contains 5 tablets) which will allow for simple and incremental dose adjustment. We will also avoid the expense of a placebo bottle. Additional information will be provided in the trial specific pharmacy inservice manual. The study coordinator at each site will be responsible for distributing the one-month supply drug kits, for verifying pill counts, for determining that there are adequate medication supplies for existing patients and new patients to be randomized. The Site PI will ultimately be accountable for administration and accountability of the medication used in this study.

The investigational drug product (clomiphene citrate and letrozole) should be stored in a secure area according to institutional and Good Clinical Practice (GCP) guidelines. It is the Investigator's responsibility to ensure that authorized and trained personnel dispense the investigational drug product.

It is the responsibility of the Investigator to ensure that a record of investigational study drug disposition is maintained at the study site where the investigational drug is stored. Record logs must comply with applicable regulations and guidelines, and should include:

- Amount received from sponsor
- Amount currently in storage
- Signatures and initials of study personnel responsible for the study drug
- A dispensing log with initials and dates of the site personnel dispensing and receiving the investigational study drug

All unused or expired study drug should be disposed of carefully, as is done with all medical waste, in accordance with institutional policy.

7.2 Concomitant Medications

An inquiry into concomitant medications will be made at the screening visit as well as each subsequent visit. Use of an exclusionary agent which affects reproductive function or metabolism, such as an anti-diabetic agent, during the study will be prohibited. A full list of these agents is found in the appendix. These medications include oral contraceptives, GnRH agonists and antagonists, antiandrogens, gonadotropins, anti-obesity drugs, somatostatin, diazoxide, insulin, and calcium channel blockers. However it is possible that the PI or other physician will prescribe progestins during the study due to abnormal bleeding/prolonged amenorrhea, which will not qualify as a reason for withdrawal. This list will be examined by the PI on a monthly basis to determine a suitable course of action. Potential interactions with study medications should also be checked.

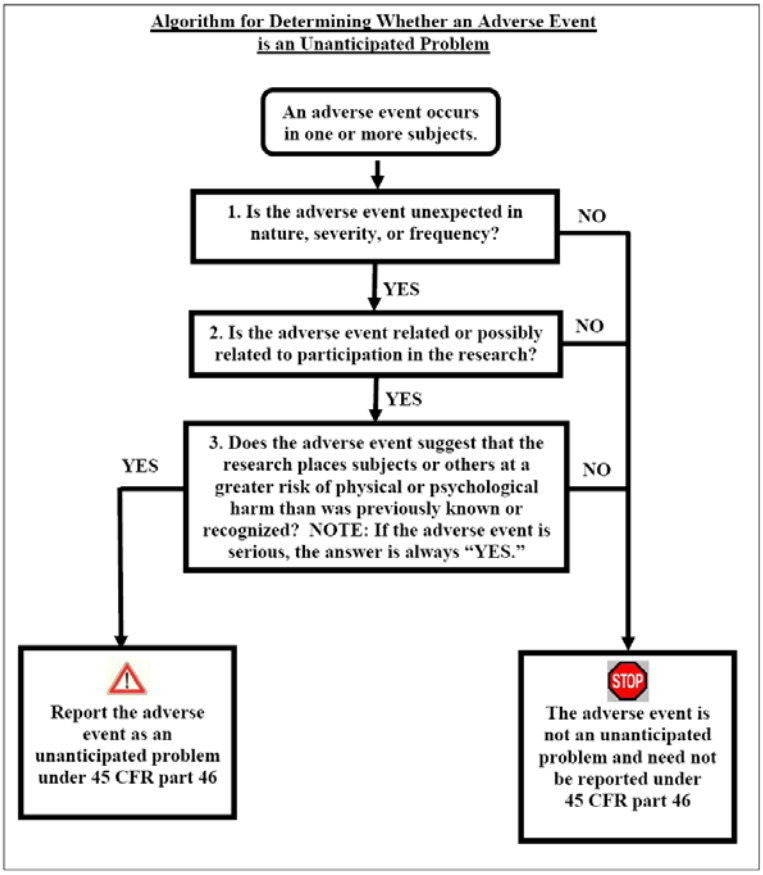
7.3 Reporting Adverse Events

All serious adverse events (SAEs) that occur from the start of study drug through thirty days after the last dose of study medication must be reported, or if the patient is pregnant, six weeks following delivery. A serious adverse event is defined as: fatal or immediately life-threatening; severely or permanently disabling; requiring or prolonging inpatient hospitalization; overdose (intentional or accidental); congenital anomaly; pregnancy loss after 20 weeks gestation; neonatal death up to 6 weeks after delivery; or, any event adversely affecting the study's risk/benefit ratio. Additionally, any event that, based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above is considered an SAE.

If an SAE occurs and is thought to be related to the study medication, the study medication will be discontinued. Twenty-four hour unblinding will be available through the web-based randomization system to break the randomization code for the individual patient if this is required by the PI for proper treatment of the patient.

The site PI will report the SAE by completing and signing the Serious Adverse Event Report Form [available in the "Study Forms" section of the RMN members-only website], and then emailing the document in PDF format to rmn-dcc@panlists.yale.edu. Subjects will be identified by study number only. No other identifying information will be included on the form. The site PI must determine and record on the SAE form whether the SAE is **unanticipated** or **anticipated**, and if it is **related**, **possibly related**, or **unrelated** to participation in the research.

DCC staff will enter the SAE information in the central database and the Safety Surveillance will analyze the SAE to determine if it meets the criteria listed in the OHRP 45CFR46 and/or FDA 21CFR312.32 & 3.14.80.



These determinations will dictate timeframes for sites' submission to the DCC, and the DCC's submission to the DSMB:

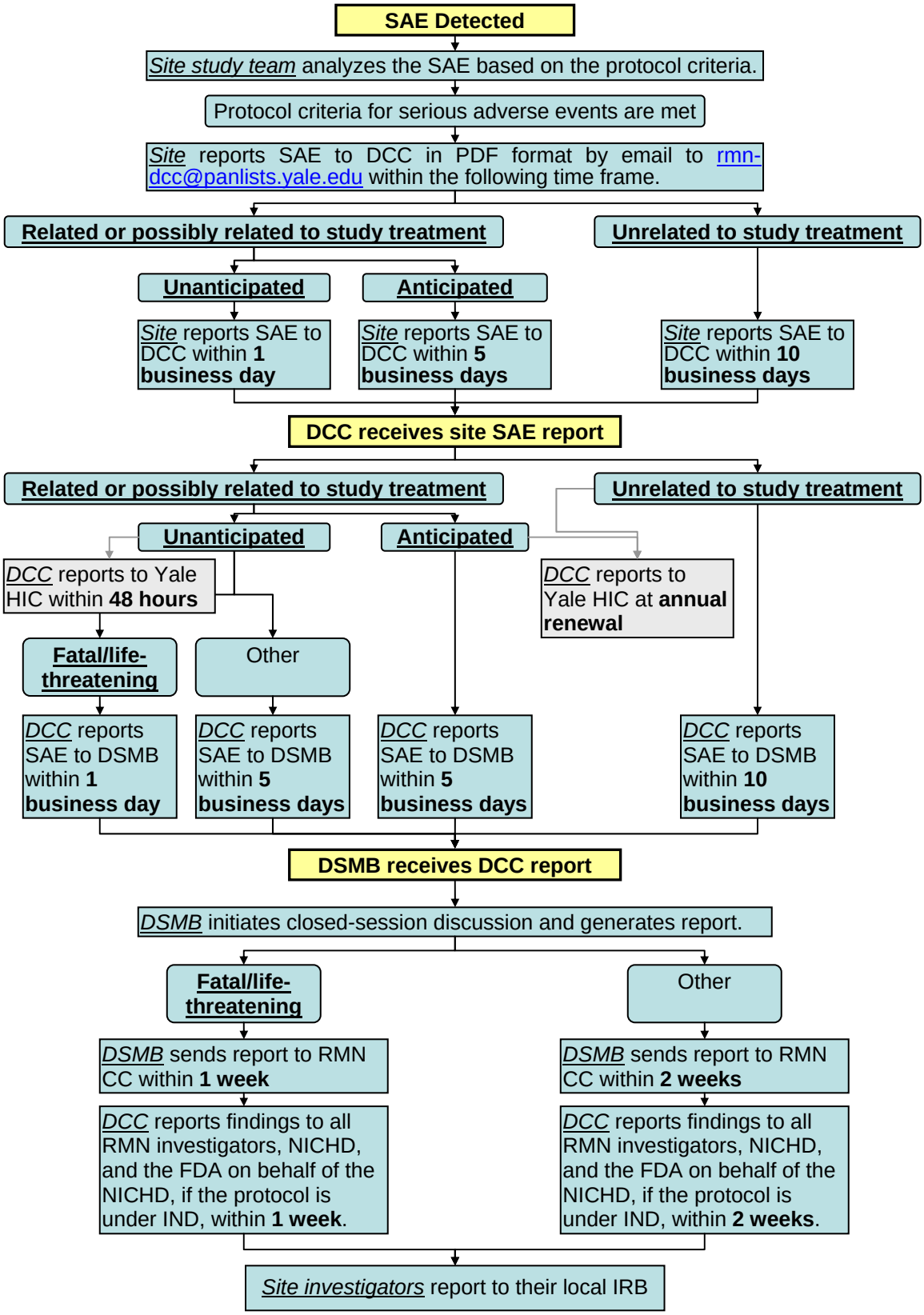
TYPE	SITE	DCC
Unanticipated and related/possibly related SAE, fatal or life-threatening	Report to DCC within 1 business day of discovery	Notify DSMB by end of next business day of receiving site report
Other unanticipated and related/possibly related SAE	Report to DCC within 1 business day of discovery	Notify DSMB within 5 business days of receiving site report
Anticipated and related/possibly related SAE	Report to DCC within 5 business days of discovery	Notify DSMB within 5 business days of receiving site report
Unrelated SAE (anticipated or unanticipated)	Report to DCC within 10 business days (no more than 3 weeks) of discovery	Notify DSMB within 10 business days (no more than 3 weeks) of receiving site report

Upon receiving notification of an SAE, the DSMB will review it via a closed-session email or conference-call discussion arranged by the NICHD RMN Committee Coordinator (RMN CC). The DSMB will send a report to the RMN CC within two weeks; reports for life-threatening SAEs will be submitted in one week. The DSMB report will include: statement indicating what related information the DSMB reviewed; the review date; the DSMB's assessment of the information reviewed; and the DSMB's recommendation, if any, for the DCC.

The RMN CC will then forward the DSMB report to the DCC for the record and appropriate disbursal. The DCC will forward reportable events to all RMN investigators, NICHD, and the FDA on behalf of the NICHD if the protocol is under IND. The NICHD Project Scientist will review, sign, and return the IND safety report to the DCC within 2 business days, and will follow up with the site PI and DCC on the SAE until it is resolved. The Protocol PI will evaluate the frequency and severity of the SAEs and determine if modifications to the protocol and consent form are required. Site PIs will report the SAE to their site IRB according to local IRB requirements. Further information is found in the RMN DSMB Communication Procedure.

Adverse events deemed non-serious will also be recorded throughout study participation from the start of study drug through thirty days after the last dose of study medication, and reported to the DCC. If an anticipated serious adverse event occurs at a frequency greater than expected, the DCC will notify the DSMB by the end of the next business day of discovery and follow the procedures for reporting serious and unanticipated and related adverse events. The DCC will forward relevant safety information to the DSMB. If an adverse event not initially determined to be reportable to the FDA under 21CFR312.32 is so reportable, the DCC will report the adverse event to the FDA within 15 calendar days after the determination is made.

A flowchart for SAEs follows:



CFR= Code of Federal Regulations

7.4 Study Medication Related Adverse Events

There are a number of adverse events that are potentially related to study medication and these will be discussed in detail for the benefit of the Advisory Board and DSMB of the RMN.

7.4.1 Clomiphene Citrate

The side effect profile of clomiphene in our double blinded double dummy PPCOS trial showed that its safety profile was acceptable and comparable to metformin, though there were increased vasomotor symptoms with clomiphene compared to the metformin arm (see Table 9 below). Clomiphene citrate should be avoided in patients with pre-existing liver disease given its hepatic metabolism. The development of visual symptoms will be a reason for discontinuing treatment although the etiology of this phenomenon is unknown. The development of persistent ovarian cysts or ovarian enlargement are also reasons for withholding further therapy.

Ovarian Hyperstimulation Syndrome (OHSS) is rare in patients receiving prescribed doses of clomiphene citrate but will be another reason to withhold further therapy. Ultrasound of the pelvis will be performed monthly and more often should the patient develop abdominal pain or other symptom suggestive of an ovarian cyst. Hot flashes (affecting 10% of patients) are common presumably due to its estrogen antagonism at the hypothalamic-pituitary axis. Mood changes are also frequently reported. Multiple pregnancy rates between 5-10%, with the vast majority of these being twins, have been reported with the use of clomiphene citrate (Asch and Greenblatt 1976 Sep). The multiple pregnancy rate among PCOS women in the clomiphene citrate arm of the PPCOS trial was 6%, with one triplet that self reduced to twins in later pregnancy. These data suggest that PCOS women will have a multiple pregnancy rate within this range, and that the risk of high order multiple pregnancy is <1%. Pregnancy complications are also common among women with PCOS as the table below indicates, but there is no evidence that there are increased risks with clomiphene. Finally there was no evidence of teratogenicity with clomiphene in the study or in the long term use of clomiphene (though a recent study discussed below suggested increased chance of CVD malformations compared to letrozole (Tulandi, Martin et al. 2006).

Table 9. Adverse Events in the PPCOS Study

	Clomiphene (N=209)	**Metformin (N=208)**	**Combination Therapy (N=209)**
Pre-Pregnancy			
Blood and lymphatic system disorders	1/209 (0.5%)	1/208 (0.5%)	0/209 (0.0%)
Cardiac disorders	2/209 (1.0%)	1/208 (0.5%)	0/209 (0.0%)
Congenital, familial and genetic disorders	0/209 (0.0%)	0/208 (0.0%)	2/209 (1.0%)
Ear and labyrinth disorders	6/209 (2.9%)	3/208 (1.4%)	1/209 (0.5%)
Endocrine disorders	0/209 (0.0%)	2/208 (1.0%)	1/209 (0.5%)
Eye disorders	8/209 (3.8%)	3/208 (1.4%)	3/209 (1.4%)
Gastrointestinal disorders	145/209 (69.4%)	177/208 (85.1%)	181/209 (86.6%)
General disorders and administration site conditions	56/209 (26.8%)	61/208 (29.3%)	61/209 (29.2%)

	Clomiphene (N=209)	Metformin (N=208)	Combination Therapy (N=209)
Immune system disorders	0/209 (0.0%)	3/208 (1.4%)	1/209 (0.5%)
Infections and infestations	40/209 (19.1%)	43/208 (20.7%)	41/209 (19.6%)
Injury, poisoning and procedural complications	4/209 (1.9%)	3/208 (1.4%)	1/209 (0.5%)
Investigations	11/209 (5.3%)	6/208 (2.9%)	7/209 (3.3%)
Metabolism and nutrition disorders	19/209 (9.1%)	37/208 (17.8%)	32/209 (15.3%)
Musculoskeletal and connective tissue disorders	31/209 (14.8%)	29/208 (13.9%)	31/209 (14.8%)
Nervous system disorders	105/209 (50.2%)	108/208 (51.9%)	106/209 (50.7%)
Pregnancy, puerperium and perinatal conditions	5/209 (2.4%)	0/208 (0.0%)	12/209 (5.7%)
Psychiatric disorders	42/209 (20.1%)	41/208 (19.7%)	40/209 (19.1%)
Renal and urinary disorders	8/209 (3.8%)	7/208 (3.4%)	13/209 (6.2%)
Reproductive system and breast disorders	94/209 (45.0%)	84/208 (40.4%)	92/209 (44.0%)
Respiratory, thoracic and mediastinal disorders	28/209 (13.4%)	24/208 (11.5%)	15/209 (7.2%)
Skin and subcutaneous tissue disorders	18/209 (8.6%)	19/208 (9.1%)	27/209 (12.9%)
Surgical and medical procedures	0/209 (0.0%)	0/208 (0.0%)	1/209 (0.5%)
Vascular disorders	58/209 (27.8%)	33/208 (15.9%)	60/209 (28.7%)

Pregnancy Related	**Clomiphene Citrate n=50**	**Metformin XR n=18**	**Combined Clomiphene and Metformin n=65**
Antepartum Complications			
Pre-term Labor	4/24 (16.7%)	1/6 (16.7%)	6/19 (31.6%)
Mild/moderate Pre-eclampsia	6/24 (25.0%)	1/6 (16.7%)	7/19 (36.8%)
Severe Pre-eclampsia/HELLP Syndrome	1/24 (4.2%)	0/6 (0.0%)	2/19 (10.5%)
Diet-controlled Gestational Diabetes (A1)	6/24 (25.0%)	1/6 (16.7%)	4/19 (21.1%)
Insulin-dependent Gestational Diabetes (A2)	3/24 (12.5%)	1/6 (16.7%)	1/19 (5.3%)
Intrauterine Growth Restriction (IUGR)	0/24 (0.0%)	0/6 (0.0%)	0/19 (0.0%)
Incompetent Cervix	1/24 (4.2%)	0/6 (0.0%)	0/19 (0.0%)
Pre-term Premature Rupture of Membranes (PPROM)	1/24 (4.2%)	1/6 (16.7%)	3/19 (15.8%)
Intrauterine Fetal Demise (IUFD)	2/24 (8.3%)	0/6 (0.0%)	2/19 (10.5%)
Other Pregnancy Complication	6/24 (25.0%)	2/6 (33.3%)	4/19 (21.1%)
Placental Abnormality	3/48 (6.3%)	1/15 (6.7%)	4/60 (6.7%)
Abruption	2/3 (66.7%)	0/1 (0.0%)	2/4 (50.0%)
Accreta	0/3 (0.0%)	0/1 (0.0%)	0/4 (0.0%)
Previa	1/3 (33.3%)	0/1 (0.0%)	1/4 (25.0%)
Other Placental Abnormality	1/3 (33.3%)	1/1 (100.0%)	1/4 (25.0%)
Any Antepartum Complications	24/48 (50.0%)	6/14 (42.9%)	19/59 (32.2%)
Post Partum			
Post-partum Depression Requiring	1/5 (20.0%)	0/1 (0.0%)	2/8 (25.0%)

	Clomiphene (N=209)	Metformin (N=208)	Combination Therapy (N=209)
Intervention			
Endometritis	0/5 (0.0%)	0/1 (0.0%)	3/8 (37.5%)
Post-partum Hemorrhage	2/5 (40.0%)	0/1 (0.0%)	0/8 (0.0%)
Other	3/5 (60.0%)	1/1 (100.0%)	3/8 (37.5%)
Any Post-partum Complication	5/48 (10.4%)	1/15 (6.7%)	8/59 (13.6%)

Pre-pregnancy adverse events were obtained from diaries and subject report to investigators, pregnancy adverse events were obtained by review of prenatal records

Other long term risks of clomiphene are uncertain. Although there have been studies suggesting that multiple cycles of clomiphene citrate may be associated with an increased risk of subsequently developing ovarian cancer (Whittemore, Harris et al. 1992 Nov 15; Rossing, Daling et al. 1994 Sep 22), many other studies have shown no effect on ovarian cancer rates (Kousta, White et al. 1997; Parazzini, Negri et al. 1998 Mar), and the current understanding is that there is probably no increased risk above and beyond those that exist for nulliparity in the case of treatment failure (Messinis 2005).

7.4.1.1 Rationale to use a dose of 150 mg a day of clomiphene citrate

This dose is used commonly clinically and doses up to 250 mg a day have been given in case series without reported serious adverse events (Lobo et al. 1982). Further we demonstrated in a post hoc analysis of the PPCOS trial that a significant portion of subjects in the clomiphene arm (8%) first responded at the dose of 150 mg (Table 10).

Table 10. Number (%) who ovulated after

CC dose	CC-only (N=150)
50 mg	95 (45.5%)
100 mg	38 (18.1%)
150 mg	17 (8.1%)

7.4.1.2 Concerns about prolonged exposure to clomiphene and decreasing cycle fecundity

We are allowing subjects with prior exposure to clomiphene to enter the trial. This raises the concern about the possible unfavorable benefit of decreased pregnancy rate after increased exposure to clomiphene. First, we did not note any time effects on pregnancy rates which remained constant per cycle for the six cycles in the clomiphene only arm (Table 6 above). Second, when we performed a post hoc analysis of pregnancy rates in the PPCOS trial we noted no significant differences in live birth rates between those subjects with prior exposure to clomiphene versus those who were drug naïve (Table 11) (Legro, Barnhart et al. 2007, *supplementary material*). These data imply that there is likely benefit in terms of live birth rates for taking clomiphene beyond 6 cycles.

Table 11. Results by treatment group stratified by previous therapy

	Previous Therapy (N=343)			No Previous Therapy (N=283)		
	Clomiphene Citrate (n=116)	**Metformin XR (n=111)**	**Combined Clomiphene and Metformin (n=116)**	**Clomiphene Citrate (n=93)**	**Metformin XR (n=97)**	**Combined Clomiphene and Metformin (n=93)**
Ovulation	272/538 (50.6%)	151/554 (27.3%)	334/559 (59.7%)	190/404 (47.0%)	145/465 (31.2%)	248/405 (61.2%)
Conception	32/116 (27.6%)	13/111 (11.7%)	39/116 (33.6%)	30/93 (32.3%)	12/97 (12.4%)	41/93 (44.1%)
Pregnancy	24/116 (20.7%)	8/111 (7.2%)	31/116 (26.7%)	26/93 (28.0%)	10/97 (10.3%)	34/93 (36.6%)
Singleton	24/24 (100.0%)	8/8 (100.0%)	30/31 (96.8%)	23/26 (88.5%)	10/10 (100.0%)	33/34 (97.1%)
Twins	0	0	1/31 (3.2%)	2/26 (7.7%)	0	1/34 (2.9%)
Triplets	0	0	0	1/26 (3.8%)	0	0
Other	0	0	0	0	0	0
Live Births	23/116 (19.8%)	6/111 (5.4%)	26/116 (22.4%)	24/93 (25.8%)	9/97 (9.3%)	30/93 (32.3%)
All pregnancy loss among patients who conceived	9/32 (28.1%)	7/13 (53.9%)	13/39 (33.3%)	7/30 (23.3%)	3/12 (25.0%)	11/41 (26.8%)
1st trimester loss	9/32 (28.1%)	7/13 (53.9%)	11/39 (28.2%)	5/30 (16.7%)	3/12 (25.0%)	9/41 (22.0%)
Biochemical or no fetal heart beat	6/31 (18.8%)	5/13 (38.5%)	8/39 (20.5%)	4/30 (13.3%)	2/12 (16.7%)	5/41 (12.2%)
Ectopic	2/31 (6.3%)	0/13 (0.0%)	0/39 (0.0%)	0/30 (0.0%)	0/12 (0.0%)	2/41 (4.9%)
Loss after observed heart beat	1/31 (3.1%)	2/13 (15.4%)	3/39 (7.7%)	1/30 (3.3%)	1/12 (8.3%)	2/41 (4.9%)
2nd-3rd trimester loss	0/32 (0.0%)	0/13 (0.0%)	2/39 (5.1%)	2/30 (6.7%)	0/12 (0.0%)	2/41 (4.9%)

Ovulation was defined by a serum progesterone level > 5 ng/ml, conception was defined as any positive serum hCG level, pregnancy defined as an intrauterine pregnancy with fetal heart motion as determined by transvaginal ultrasound, and live birth defined as delivery of any viable infant.

7.4.2 Letrozole

Letrozole has been tolerated across all studies in first-line and second-line metastatic breast cancer as well as extended adjuvant treatment in women who have received prior standard adjuvant tamoxifen treatment. The most common side effects compared to placebo are usually hot flashes, arthralgia/arthritis, and myalgia. Unfortunately, the data using letrozole for infertility

have not been systematically collected and reported. However head to head trials of letrozole and tamoxifen (a triphenylethylene derivative similar to clomiphene) may provide insight into the expected side effect profile between the two medications. Fatigue and dizziness has been also seen with the use of Letrozole, so caution is advised when driving or using machinery.

8010 women with early breast cancer were randomized to either letrozole or tamoxifen in the BIG I-98 study published in the NEJM (Thurlimann, Keshaviah et al. 2005). We will directly quote from the safety results from this trial. The key safety findings were that thromboembolism, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group. Women given letrozole had a higher incidence of skeletal and cardiac events and of hypercholesterolemia (See table 3 below from the NEJM paper reproduced below).

More patients in the letrozole group than in the tamoxifen group reported at least one protocol-specified adverse event of any grade (2912 patients vs. 2554 patients), but the number of patients with life-threatening or fatal protocol-specified adverse events was similar in the two groups (67 of 3975 [1.7 percent] and 69 of 3988 [1.7 percent], respectively). Fractures were significantly more frequent in the letrozole group than in the tamoxifen group (5.7 percent vs. 4.0 percent, P<0.001), with a significantly shorter time to a first fracture reported within four weeks after the end of treatment (P<0.001). As compared with tamoxifen, letrozole was associated with fewer thromboembolic events (1.5 percent vs. 3.5 percent, P<0.001), a lower rate of vaginal bleeding (3.3 percent vs. 6.6 percent, P<0.001), fewer endometrial biopsies (72 of 3089 women [2.3 percent] vs. 288 of 3157 women [9.1 percent], P<0.001), and fewer invasive endometrial cancers (4 of 3089 women [0.1 percent] vs. 10 of 3157 women [0.3 percent], P=0.18). The respective median changes in cholesterol values from baseline to 6, 12, and 24 months were 0, 0, and –1.8 percent in the letrozole group and –12.0, –13.5, and –14.1 percent in the tamoxifen group. A total of 43.6 percent of patients in the letrozole group and 19.2 percent of patients in the tamoxifen group had hypercholesterolemia reported at least once during treatment (grade 1 in 35.1 percent and 17.3 percent, respectively). The overall incidence of adverse cardiovascular events of grade 3, 4, or 5 was similar in the two groups (3.7 percent in the letrozole group and 4.2 percent in the tamoxifen group), but more women in the letrozole group had grade 3, 4, or 5 cardiac events (2.1 percent vs. 1.1 percent, P<0.001).

Table 3. Incidence of Worst Grade of Adverse Events among Patients Included in the Safety Analysis.*

Adverse Event	Letrozole (N=3975)						Tamoxifen (N=3988)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	number of patients (percent)										
Cerebrovascular accident or TIA	ND†	ND†	20	15	4	39 (1.0)	1‡	ND†	22	17	1
Thromboembolic event	13†	17	22	7	2	61 (1.5)	17†	40	54	27	2
Cardiac event	51	26	50	19	16	162 (4.1)	83	26	27	12	5
Ischemic heart disease	5	9	24	13	6	57 (1.4)	14	9	13	8	2
Cardiac failure	4	9	6	3	9	31 (0.8)	5	4	2	2	1
Other cardiovascular event	11	3	2	3	0	19 (0.5)	4	0	3	0	1
Vaginal bleeding	114	16	2	0	0	132 (3.3)	198	61	4	0	0
Hot flashes	687	645	ND†	ND†	ND†	1332 (33.5)	704	812	ND†	ND†	ND†
Night sweats	295	259	ND†	ND†	ND†	554 (13.9)	313	334	ND†	ND†	ND†
Fracture	ND†	148	77	ND†	ND†	225 (5.7)	ND†	113	46	ND†	ND†
Arthralgia	467	263	74	2	0	806 (20.3)	289	166	35	1	0
Myalgia	156	72	25	1	0	254 (6.4)	176	50	16	1	0

* Adverse events were recorded during or within 28 days after study treatment. The adverse events reported in the table were recorded by the checking of speci report forms, except in the case of arthralgia and myalgia, which were recorded in an "other" category and thus may have been underestimated. Grades were the Common Toxicity Criteria of the National Cancer Institute (version 2.0), if available, and according to criteria defined by a senior IBCSG oncologist in the Fisher's exact P values are reported for the comparison of any grade and are not adjusted for multiple comparisons. TIA denotes transient ischemic attack.

† The grade was not defined (ND) according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0); nevertheless, grade 1 thromboemb and confirmed by investigators.

‡ This patient had a grade 1 cerebral microangiopathy.

7.4.3 Letrozole and Animal Reproductive Toxicity Studies

The following information has been obtained from the FDA approval summary of letrozole (Cohen et al. 2002).

Division of Oncology Drug Products (HFD-150), Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland 20857, USA. cohenm@cder.fda.gov: In subacute toxicology studies (14 days to 3 months), females of all species showed signs of estrogen deprivation, including disturbed estrous cycle, cystic and atretic ovarian follicles, decreased uterine weight, and vaginal atrophy. As the letrozole dose and length of drug exposure increased, the severity of these signs increased. In males of each species, signs of testosterone deprivation (presumably secondary to increased luteinizing hormone release inhibiting pituitary gonadotropins) occurred, including decreases in hemoglobin, decreases in testicular weight, somniferous tubular atrophy, epididymal oligospermia, and testicular interstitial cell hyperplasia.

With longer dosing (3 months to 1 year) in the rat and dog, additional changes were noted. In females, ovarian interstitial cell hyperplasia, mammary duct gland hyperplasia with increased secretions, decreased bone density, adenopituitary hyperplasia, hypertrophy of thyroid follicular

cells, thymic atrophy, increase in serum cholesterol, elevated liver enzymes, and hepatocellular hypertrophy were observed. In males, prostatic atrophy, decreased mammary gland proliferation, decreased bone density, and adenopituitary hyperplasia also occurred. In both species, higher drug doses were associated with hepatic and renal tubular damage, the latter apparently related to hypercalcemia because of bone resorption.

Two-year murine carcinogenicity studies showed an increased rate of benign ovarian theca cell tumors at doses > 60 mg/kg (180 mg/m^2) and a decreased rate of benign and malignant mammary gland tumors. In reproductive toxicology studies, maternal toxicity was reported at all doses, with embryo and fetal toxicity at doses 0.03 mg/kg (0.09 mg/m^2). In the rat study, comparable toxicity was observed at doses of 0.03 mg/kg (0.18 mg/m^2). Similar findings were observed in rabbits at doses 0.066 mg/m^2. Mutagenicity testing was negative.

7.4.4 Letrozole and the Fetus

These serious adverse events (Thromboembolic events, endometrial cancer, and osteoporotic fractures) are extremely less likely in premenopausal women with PCOS, and overall we find the safety profile of letrozole comparable to clomiphene. The primary concern is the safety of the medication during pregnancy. Though we have no intentions to give the medication during pregnancy, and we have established safeguards (see the protocol above and discussion below), this is a major concern. In November of 2005, Novartis of Canada issued a black box warning about the potential teratogenecity of letrozole (again, that data has not been published in a peer reviewed journal, so it is not possible to assess its strength or quality). Their public announcement is reproduced below:

PUBLIC COMMUNICATION
Health Canada Endorsed Important Safety Information on
Femara*(letrozole)

NOVARTIS

November 24, 2005

Subject: Femara* (letrozole) should not be used in women who may become pregnant

Femara* (letrozole) is a medication authorized for use in Canada to treat breast cancer in women who are postmenopausal. Novartis Pharmaceuticals Canada Inc. ("Novartis") as the manufacturer and distributor of Femara* (letrozole), is aware that Femara* is being used to stimulate ovulation in women who are infertile, or unable to become pregnant, as a treatment to increase their chances of becoming pregnant. Novartis believes it is our responsibility to remind physicians treating infertility and their patients that:

- Femara* is authorized for use in post-menopausal women with breast cancer only.
- The use of Femara* for the purpose of inducing ovulation and increasing the chance of pregnancy is **not** an authorized use of this drug.
- Femara* is contraindicated and should not be used in women who may become pregnant, during pregnancy and/or while breastfeeding, because there is a potential risk of harm to the mother and the fetus, including risk of fetal malformations.
- If there is exposure to Femara* during pregnancy, the patient should contact her physician immediately to discuss the potential of harm to the fetus and potential risk for loss of the pregnancy.

Novartis has also issued a letter to Canadian obstetricians, gynecologists and fertility specialists advising them of this safety information. This letter can be found on the Health Canada website at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html

Novartis is committed to the delivery of quality pharmaceutical products and to ensuring the timely communication of safety information that is important to patients and health care professionals.

If you have questions about your current prescription, please contact your physician or pharmacist.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious or unexpected adverse reactions in patients receiving Femara* should be reported to Novartis or Health Canada at the following addresses:

In response, 5 Canadian fertility centers reviewed their birth outcomes and incidence of congenital malformations on letrozole and compared them to clomiphene (Tulandi, Martin et al. 2006). It is important to note that these same investigators have pioneered and advocated the use of letrozole as an ovulation induction adjuvant, and thus have a potential conflict of interest. However these data are invaluable for evaluating the fetal safety of exposure to this medication (and to clomiphene) and are reproduced in some detail to allow the AB and DSMB to assess the feasibility of such a study.

The Canadian study involved 911 newborns from women who conceived following CC or letrozole treatment, and involved examination of medical files of both mother and newborn, and cross-checked with the parents by telephone calls (Tulandi, Martin et al. 2006). Overall, congenital malformations and chromosomal abnormalities were found in 14 of 514 newborns in the letrozole group (2.4%) and in 19 of 397 newborns in the CC group (4.8%). The major malformation rate in the letrozole group was 1.2% (6/514) and in the CC group was 3.0% (12/397). One newborn in the letrozole group was found to have a ventricular septal defect (0.2%) compared to 4 newborns in the CC group (1.0%). In addition, the rate of all congenital cardiac anomalies was significantly higher (P: 0.02) in the CC group (1.8%) compared to the letrozole group (0.2%). The authors concluded that there was no difference in the overall rates of major and minor congenital malformations among newborns from mothers who conceived after letrozole or CC treatments. However, it appears that congenital cardiac anomaly is less frequent in the letrozole group. The concern that letrozole use for ovulation induction could be teratogenic is unfounded based on our data.

Other manufacturers feel differently about aromatase inhibitors judging by the commitment of Serono to undertake Phase II studies of anastrozole, and while anastrozole may have different reproductive and fetal risks than letrozole, this has not yet been established. Obviously a study of the size proposed in this protocol will have low power to detect rare congenital malformations; however, it is a needed start. ***Overall, our review of the available evidence suggests that the risk benefit ratio for using letrozole is comparable to clomiphene for both mother and fetus, and that from a safety standpoint, the risk is acceptable.***

7.5 Protection against Risk of Study Interventions

7.5.1 Clomiphene

Subjects will be warned about potential mood changes and visual changes on clomiphene. Visual changes, which may be due to enlargement of the pituitary and pressure on the optic chiasma is a reason for immediate evaluation and usually discontinuation of clomiphene. We will also monitor closely for signs of a deep venous thrombosis or other signs of altered blood coagulation. Subjects will be monitored by monthly ultrasound for the formation of ovarian cysts. This was not a significant area for AEs in the PPCOS study, but we did not perform routine ultrasound monitoring. Subjects will also be monitored for abnormal thickening of the endometrium, and withdrawal bleed will be induced with progestin, or further testing (i.e. endometrial biopsy) performed at the discretion of the investigator.

7.5.2 Letrozole

Subjects will be warned about the potential for hot flashes, arthalgias, and myalgias. Dysfunctional uterine bleeding will be assessed by the investigator with exam, ultrasonography,

and endometrial biopsy as needed. Subjects will also be monitored for abnormal thickening of the endometrium, and withdrawal bleed will be induced with progestin, or further testing (i.e. endometrial biopsy) performed at the discretion of the investigator. We will also monitor closely for signs of a deep venous thrombosis or other signs of altered blood coagulation. Subjects will be monitored by monthly ultrasound for the formation of ovarian cysts.

7.6 Preventing Exposure to Study Drug During Pregnancy

A urine pregnancy test will be performed at all study visits except for the menses visits. In addition, a serum pregnancy test will be performed at screening and baseline visits. We have also instituted a monthly menses visit which will consist of a serum pregnancy test at the time of menses or missed menses. This will prevent unintended exposure of an early unrecognized pregnancy to study medication. Subjects will also be dispensed pregnancy tests to test themselves should they suspect they are pregnant. Study medication will be dispensed on a monthly basis, but only for that next cycle; therefore, if subjects fail to come to the monthly visit, they will not receive study drug for the next cycle.

7.6.1 Pregnancy Complications

Subjects will be followed through the study after a positive pregnancy test to confirm the location and viability of the pregnancy before being released to their Ob/Gyns. It is possible that a pregnancy may be nonviable or an ectopic pregnancy and require further medical or surgical therapy to treat. Subjects will have the option to pursue concurrent care with their personal physician in the early phases, but our experience with PPCOS was that subjects followed up with us until fetal heart motion was noted on transvaginal ultrasound exam. We are also establishing a pregnancy registry to document all fetal losses and maternal and neonatal morbidities as discussed above.

7.7 Data Collection and Management (including quality assurance/compliance measures)

7.7.1 Data Entry and Forms

Case Report Forms (CRFs) will be developed as the protocol is developed. They will also be implemented in a Web-based Oracle data management system. The Web data entry forms will be implemented to be similar to the paper forms with the same questions. However, the Web forms usually have more flexibility than the paper forms, such as pull down menus.

7.7.2 Features of Data Management System

Features of the data management system include study definition; different types of data entry (including double entries and complete audit trail); forms control; query capture, reporting, and resolution; dictionary coding of Adverse Events (AEs) and medical terms; clinical data review tools; 21 CFR Part 11 and CDISC compliant; and prepares data and CRF images to FDA e-Submission Standards. The end-user/reporting/ad hoc query front-end uses a standard Web browser, so that data entry and browsing can be done from any machine with Internet access, without purchase of special software. Login to this system will be through a secured Web server with the security under the protection of the Yale Data Center.

7.7.3 Data Security

A data server and Web server will be used. These two servers will be separated and managed by Yale University ITS Data Center. The web server will be accessible through a secured login, but the data server can only be accessed through the web server. For security purposes, no login to the data server will be permitted. PHI, including patient names and addresses, will be locked and secured at the participating sites, and data will be linked through a unique identification number, which will be assigned after a patient is screened or enrolled. Access will be limited to authorized individuals (21 CFR 11.10(d)). Each user of the system will have an individual account. The user will log into the account at the beginning of a data entry session, input information (include changes) on the electronic record, and log out at the completion of the data entry session. The system will be designed to limit the number of log-in attempts and record unauthorized access log-in attempts. Individuals will work only under their own access key, and not share these with others. The system will not allow an individual to log onto the system to provide another person access to the system. Access keys will be changed at established intervals commensurate with a documented risk assessment. This plan has been adapted from the guidelines for computerized systems used in clinical investigations established by the U.S Department of Health and Human Services Food and Drug Administration.

7.7.4 Data Quality Control

- ***Competency to Perform Procedures/Tests in the Protocol***

The site PI will be responsible for ensuring that study related tests are performed by competent personnel. The criteria for determination of competency may vary between sites in the study.

- ***Quality Control Steps***

Quality control of data will be handled on three different levels. The first level is the real-time logical and range checking built into the web-based data entry system. The research coordinators and data entry clerks at the participating sites are required to ensure the data accuracy as the first defense. The second is the remote data monitoring and validation that is the primary responsibility of the data manager and programmer at the DCC. The data manager will conduct monthly comprehensive data checks (SAS programs run on a regular basis as a systematic search for common errors and omissions), as well as regular manual checks (within the database system). Manual checks will identify more complicated and less common errors. The data manager will query sites until each irregularity is resolved. The third level of quality control will be the site visits, where data in our database will be compared against source documents. Identified errors will be resolved between the DCC and clinical sites. The visits will assure data quality and patient protection.

An audit trail will be added as another security measure. This will ensure that only authorized additions, deletions, or alterations of information in the electronic record have occurred and allows a means to reconstruct significant details about study conduct and source data collection necessary to verify the quality and integrity of data. Computer generated, time-stamped audit trails will be implemented for tracking changes to electronic source documentation.

Controls will be established to ensure that the system's date and time are correct. This is a multi-center clinical trial and will be located in different time zones. System documentation will explain time zone references as well as zone acronyms. Dates and times will include the year, month, day, hour, and minute to the date provided by international standard-setting agencies (e.g.

US National Institute of Standards and Technology). The ability to change the date or time will be limited to authorized personnel, and such personnel will be notified if a system date or time discrepancy is detected.

In addition to internal safeguards built into the computerized system, external safeguards will be implemented. Data will be stored at the Data Coordination Center. Records will be regularly backed up, and record logs maintained to prevent a catastrophic loss and ensure the quality and integrity of the data. This plan has been adapted from the guidelines for computerized systems used in clinical investigations established by the U.S Department of Health and Human Services Food and Drug Administration.

7.8 Study Monitoring

A monitoring plan that satisfies the Guideline for Monitoring of Clinical Investigations of the National Cancer Institute will be used. A Project Manager from the DCC will lead this effort, and report findings to the DCC PI. The Project Manager will have full knowledge of the study protocol, Manuals of Procedures, and is familiar with the database system and is trained to review patient charts. The Project Manager will be responsible for training and supervising other personnel.

Once personnel at a participating site are trained to recruit patients, the Project Manager will be sent to the site to help initiate the study according to the study protocol, and to ensure that the clinical site meets the scientific, clinical, and regulatory requirements. For example, the Project Manager will review all signed and dated forms required by the FDA (such as financial disclosure forms), the curriculum vitae and certifications of the investigators and personnel, CRF training, and the written IRB approval of the protocol and consent form.

The on-site monitor will return to the clinical site after a defined number of patients are recruited (can be as early as the recruitment of the 2nd patient) or a certain time period has passed, depending on the enrollment duration of the protocol execution. The schedule of visits will be discussed and agreed in the Steering Committee and we anticipate that the Project Manager will visit each participating site at least once.

During the site visit, the clinical sites should provide to the monitor a space and access to all relevant records including medical records and regulatory binders, and there would be immediate verbal feedback provided to the site after original source documents are compared to entries in the CRF. The clinical sites must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. The on-site monitor will conduct an audit of a random sample of entered information against the source documents, a review of all regulatory documents, a review of all informed consents, and a review of all pharmacy logs. The clinical site PI and coordinator should be available to meet the monitor during the visit. The monitor will review electronic data from all sites, providing a method for identifying systematic errors or problems.

To assure Good Clinical/Laboratory Practice, the monitor will control adherence to the protocol at the clinical sites and evaluate the competence of the personnel at the clinical sites including the ability to obtain written informed consents and record data correctly. The monitor will inform the DCC PI, the Steering Committee, and NICHD regarding problems relating to facilities, technical equipment, or medical staff. A thorough written report will follow each site-visit and will include a detailed itemization of discrepancies and items requiring follow-up or reconciliation. This report will also be forwarded to the Steering Committee for review. The

monitor will be responsible for maintaining regular contacts between the investigators in the clinical sites and the RMN. When the study ends, the monitor will also visit the clinical site to provide assistance for close-out.

7.9 Data and Safety Monitoring Board

The NICHD has established an independent Data and Safety Monitoring Board (DSMB) to review and interpret data generated from RMN studies and to review protocols prior to their implementation. Its primary objectives are to ensure the safety of study subjects, the integrity of the research data and to provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN. The DSMB advises on research design issues, data quality and analysis, and research participant protections for each prospective and on-going study. A copy of the DSMB Charter can be found in the appendix.

The DSMB members are appointed by the Director of NICHD in accordance with established NIH and NICHD policies. DSMB members are experts in and represent the following fields: biostatistics, epidemiology, infertility, gynecology, andrology and ethics. The NICHD Committee Coordinator is responsible for scheduling regular committee meetings, recording all meeting minutes and summarizing the committee recommendations for the Steering Committee and NICHD. Steering Committee members are prohibited from attending closed sessions of the DSMB. Open sessions may be attended by Steering Committee members or Chairperson when requested by NICHD and the DSMB.

The DSMB meets regularly at a time and place of their choosing to review Network randomized trial protocols with respect to ethical and safety standards, monitors the safety of on-going clinical trials, monitors the integrity of the data with respect to original study design, and provides advice on study conduct. The DSMB periodically monitors data quality, including protocol adherence and adverse events. As outlined in the protocols, the DSMB will conduct regular evaluations of the data. It may recommend protocol modifications based on concern for subject welfare and scientific integrity.

7.10 Reporting

Administrative Reports will be prepared by the DCC, and they include monthly and quarterly reports to the RMN on accrual, data quality and study compliance and reports presented in the packet produced for each Steering Committee (SC) and DSMB. Statistical reports include reports to the SC and AB from the data analysis, and special reports for scientific manuscripts.

Statistical Reports will be generated in SAS. Reports are provided for DSMB reviews, and for final analysis of study results in preparation for scientific publications. The content of these reports will be very complete, and will serve as the template for the final report of each study, which in turn will form the basis of the publication of the results. Our proposed reports to the DSMB would include the following: a protocol description and history; accrual rates; site performance in terms of accrual; eligibility; protocol violations; data accuracy and minority representation; patient characteristics by treatment and site; and the rate of adverse experiences.

7.11 Obligation of the Investigator

7.11.1 IRB Review

The site PI is responsible for submitting the approved protocol and consent form to the local IRB for review. The IRB must approve all aspects of the study as detailed in the protocol, including

the patient informed consent form. It is anticipated that there will be minor site-specific changes in the consent form. The IRB must periodically review the status of the study at appropriate intervals not exceeding one year. The site PI will also be responsible for submitting revisions to the protocol to the IRB and promptly communicating serious adverse events that result during the study. After the approval, the informed consent and IRB approval (or amendment) letters must be forwarded to the DCC.

7.11.2 Maintenance/Retention of Site Records

In order to comply with Good Clinical Practice (GCP) requirements, the investigators must maintain the master patient log that identifies all patients entered into the study for a period of two years after the study ends so that the subjects can be identified by audit. The PI must maintain adequate records pertaining to subjects' files and other source data for a minimum of 5 years after completion of the study.

7.12 Regulatory Requirements

The DCC will work with NICHD staff by providing them with clinical study data, reports, and other support as required for AE Reporting and IND submissions. The Project Managers will work with NICHD colleagues in meeting all regulatory requirements including compliance with ICH and HIPAA requirements, FDA code for federal regulations (Title 21), and IND applications. For example, the DCC Project Managers will register this clinical trial timely with ClinicalTrials.gov via a web based data entry system called the Protocol Registration System (PRS).

7.13 Protocol Amendments

Once the protocol is approved by the Steering Committee, it is then reviewed by an Advisory Board and Data and Safety Monitoring Board (DSMB). After all approvals, the DCC will finalize the protocol document that serves as the agreement among all members of the Network. In the meantime, because Yale administers all patient care costs for the RMN, Yale will promptly issue subcontracts to the participating sites based on the cost agreements made by the Steering Committee and NICHD.

After the protocols are approved by the RMN and the Steering Committee decides that changes are necessary for scientific or clinical reasons, the DCC will facilitate the procedure timely and diligently. The RMN investigators and key personnel will participate in teleconferences and meetings, discuss, vote, and document circumstance and rationales for the changes and the implementation procedure for the changes. These include revising study hypotheses, designs, sample sizes, data entry forms, and appropriate statistical analyses. Once the amendments are finalized and agreed to by the RMN, they will be submitted to the IRB and DSMB reviews and approvals.

8 Publication Policy

8.1 Overall Policy

The publications policy proposes guidelines for publications that originate from our collaborative Reproductive Medicine Network. Decisions concerning publications shall be determined by consensus (majority vote) of the collaborating principal investigators (or designate) noted below as the "Network". This policy is designed to promote prompt, exact, quality publications and presentations of Network studies with appropriate academic recognition of those with significant contributions. Protocols are classified into three types: 'Main Study' (which may include major and minor publications), 'Ancillary Study', and 'Pilot Study'. Additionally there may be publications from concepts or ideas generated by the RMN ("Related Publications") or from other groups utilizing RMN data and/or specimens "Outside Studies" (those utilizing data and/or specimens from the RMN studies). Abstract submissions to national meetings will also follow the publications policy below. The progress of publications (including presentations) will be a standing agenda note on all phone conferences and meetings. The Steering Committee will make the final disposition regarding disputes with respect to analysis request approval, prioritization, presentation, authorship and/or manuscript submission.

8.2 Main Study

A Main Study is a Network study designed prospectively by an investigator independent of other studies. Generally that investigator becomes Lead investigator of the protocol and Chair of the Protocol Subcommittee. At the end of each Main Study, a primary analysis resulting in the primary manuscript and a number of secondary analyses is produced based on the research questions stated in the protocol. The Protocol Subcommittee Chair is the primary author of the primary analysis. A main study can generate major (related to the major hypotheses) and minor publications (relating to secondary hypotheses).

8.2.1 Major Publications

A major publication is defined as one reporting results of the major hypotheses tested. (For example, does hMG/IUI increase cyclic fecundity in couples with unexplained or male factor infertility?).

1. Authorship: Publications will include the names of investigators from each RMU and the DCC rather than merely identify the "Reproductive Medicine Network". Each RMU and DCC will have up to two authors per publication, ordinarily the PI and the Co-PI, but this may at times involve another investigator who has contributed to the study at their site, in lieu of the PI or Co-PI. The principal investigator at each RMU will be responsible for submitting the names of the two authors from that unit and designating them as either the primary and secondary authors of the unit. No more than 2 authors may represent a RMN site. An ancillary site (such as a SCCPIR) may only have 1 investigator.

The Steering Committee Chair and NIH Project Scientist will be authors. Occasionally, additional authors, both within and outside the RMN may be appropriate. In these cases, the final decision will be by Network consensus (majority vote of the steering committee required).

2. First Author: The lead investigator initiating the protocol, chairing the Protocol Subcommittee will be the first author. The first author would always be expected to prepare the initial draft of the manuscript, after receiving approval from the Network to proceed. The author will prepare the first draft of the manuscript in a timely fashion after receiving all the relevant data analyses from the DCC. The primary author will circulate the final draft to all authors prior to submission, with a timely turnaround of comments from other authors expected. Final decision of the manuscript content will be determined by the Protocol Subcommittee. In the event that the initiating protocol investigator declines first authorship or fails to meet the timeline determined by the Steering Committee (as determined by majority vote) and monitored monthly, the next RMU investigator in the rank order of authors (described below) will be the first author.

3. Authorship Order: All authorships are expected to meet reasonable criteria as set forth by (International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. http://www.icmje.org. Updated February 2006. Accessed April 4, 2007.) The overall authorship order will be 1) the primary author, 2) RMU investigators, additional outside investigators with a limit of one author per site (e.g. SCCPIR investigators if applicable), followed by the Steering Committee Chair, NIH Project Scientist, and then the authors of the DCC.

Authorship Order Category	Description
1	Lead Investigator of the Protocol (N =1)
2	Primary RMN Investigators of the Protocol (N = 6); DCC Investigator (N = 1)
3	Outside Investigators (i.e. Primary investigator of SCCPIR sites) (N = to be determined)
4	Additional Investigators (by Steering Committee vote) (N = to be determined)
5	Secondary RMN Investigators (N = 7)
6	Steering Committee Chair (N = 1)
7	NIH Project Scientist (N = 1)
8	DCC PI (N = 1)
9	"for the NICHD Reproductive Medicine Network"

It is anticipated there will be up to 18-25 authors per major manuscript. The authorship order of the RMUs and outside sites will be based upon subject recruitment, data accuracy and promptness of data report according to the chart below:

Investigative Sites	# Subjects Rank	Accuracy Rank	Total Rank	Authorship Order
A	1	4	5	3
B	2	7	9	6
C	3	1	4	2
D	4	2	6	4
E	5	3	8	5

F	6	5	11	7
G	7	6	13	8

Data accuracy will be ranked according to the rate of missing or false data entries/randomized subject at each site. Inquires that show data was accurately entered will not count against this rate of data inaccuracy. Each site's PI will be responsible to document the contributions to the study of that site's authors. In the event the journal editor requires fewer authors even after written documentation of the authors' contribution has been provided, the steering committee will vote on the authorship order which will include at a minimum the Lead Investigator and PI of the DCC (or his/her designate) in the positions listed above with the authorship order ending with the footnoted statement "for the Reproductive Medicine Network". The other authors will be referenced in the footnote and listed in the title page.

4. Acknowledgement Section: The acknowledgement section will include other investigators and study personnel who contributed substantially to the study by site, as well as members of the Advisory Board and the Data and Safety Monitoring Board. The designation will list the initials of the individual followed by their highest degree (e.g. C. L. Gnatuk, J.L. Ober, R.N., etc.). Significant contributions include but are not limited to protocol review, initiation and participation at each site, subject recruitment and enrollment, study conduct, data analysis, and preparation of the manuscript.

8.2.2 Minor Publications

Minor studies are defined as those in which the hypotheses would not be the main elements of Network studies, but in which the study data base would be utilized to test secondary hypotheses. (One example would be testing whether metformin use spares the dose of clomiphene resulting in lower dose needs.) Ideas for "minor studies" will, in general, be proposed by a single individual, who would direct all efforts leading to publication and representation. The results from minor studies would be handled similarly to those from major studies. The "Protocol" is defined as the Concept Protocol/study design of the hypothesis resulting in the publication.

Authorship will follow the Major publications guidelines above with the exception that the individual leading the minor study would be the first author, followed by the ranked primary RMN investigators involved in developing the Concept Protocol. The Lead Investigator of the minor publication can propose additional investigators who contributed to the study, whose inclusion in the authorship will be voted on by the Steering Committee (majority vote of SC required for inclusion in authorship). Centers may wish to withdraw inclusion from authorship of publications of minor studies in which only data are contributed, and this will be the decision of the individual site (RMU) PI.

8.3 Ancillary Study

An Ancillary Study is an observational study, conducted as a supplement to a Main Study, and will have a separate written protocol. By definition, an Ancillary Study involves all or a subset of patients enrolled in a Main Study. An Ancillary Study does not involve any additional participants. To be defined as an Ancillary Study, there must be a need for collection of additional data not already collected in the Main Study. An Ancillary Study may also be

designed by another Network investigator, who would serve as the lead investigator and primary author of the paper. Ancillary Studies may be a "single-center" or "multi-center".

A "single-center" Ancillary Study is a study in which all data are collected, stored and analyzed at a single center. The center bears the additional cost of such a study. The study requires approval of the Main Study Protocol Subcommittee and the Steering Committee. The center conducting the study is responsible for the analysis and reporting of the results. Abstracts and manuscripts resulting from data from the single-center Ancillary Study are not subject to the RMN Publications Policies.

A "multi-center" Ancillary Study is defined as one for which data or material (such as specimens) are collected at more than one center, or additional funds for conduct of the study are provided by the NICHD RMN and the DCC provides data analysis. Multi-center Ancillary Studies require the approval of the Main Study Protocol Subcommittee and the Steering Committee.

Authorship will be as per Major publications above with the exception that the individual leading the ancillary study and writing the paper would be the first author, followed by ranked RMN primary investigators, etc. A center not participating in the ancillary study would not receive authorship unless by majority vote of the steering committee.

8.4 Pilot Study

A Pilot Study is a preliminary study that generates data to help in the design of a Main Study and is the responsibility of the Main Study Protocol Subcommittee. The DCC collaborates with the Protocol Committee to complete the analysis, which may or may not generate an abstract for presentation and/or a manuscript for publication. The DCC writes a Final Report if there is sufficient data to justify one. It is not expected there will be any secondary analyses resulting from a Pilot Study.

8.5 Related Publications

A related publication is one that has had significant input from members of the RMN Steering Committee at formal meetings in terms of study significance and design. It is distinct from an ancillary publication in that a related publication reports on a study, concept or new methodology that has not been subjected to formal DSMB review and approval. Generally, "Related Publications" will arise from ideas and studies discussed with the Steering Committee, but not voted upon to become formal protocols.

The investigator who initiates, conducts and writes the study and those who (s)he names will be the sole authors. The authors should acknowledge the contribution of the NICHD Reproductive Medicine Network in the author line of the publication according to the format of the journal.

8.6 Outside Studies

Outside studies will result from the sharing of intellectual property, data and/or specimens with investigators whose protocols have been approved by the steering committee, and who comply with all components of those policies. All publications will acknowledge the assistance of NICHD, the RMN, and the Protocol Subcommittee in making the database available on behalf of the project. In addition, however, a disclaimer will need to be included stating, "The contents of this report represent the views of the authors and do not represent the views of the NICHD Reproductive Medicine Network." The authors will be requested to cc the submitted manuscript

to the NICHD program official to ensure compliance. These policies apply to both Network centers and outside centers.

8.7 Presentations

Network data should be presented before national organizations by the lead investigators of Main Studies, Ancillary, and Pilot studies. Organizations that might be appropriate include the American Society of Reproductive Medicine, the Society for Gynecologic Investigation, the American College of Obstetricians and Gynecologists, the American Urology Society and other urology or andrology societies. All presentations will be approved by the P & P committee. Once data are published in at least abstract form, all members of the Network can cite them publicly in lectures.

However, investigators should avoid citing specific numbers in review articles and chapters, for this could jeopardize peer review publication. Authorship, First Author, and Author Order are as described for Major Publications, and if there is an authorship limit to the abstract we will follow the plan above under Major Publications. Oral and poster presentations, including those resulting from secondary analyses at professional societies, must list all authors and participating institutions. In addition, they must include both the NICHD RMN logo and NIH Department of Health and Human Services logos that can be found on the Network web site.

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10 Human Subjects/Informed Consent

SAMPLE CONSENT FORM - FEMALE

This form is not valid unless this box includes an approval stamp by the IRB

CONSENT FOR RESEARCH
[insert institution name].

Title of Project: Pregnancy in Polycystic Ovary Syndrome II (PPCOS II):
A 25-week, Double-Blinded, Randomized Trial of Clomiphene Citrate and Letrozole for the Treatment of Infertility in Women with Polycystic Ovary Syndrome

Principal Investigator: *[insert site principal investigator]*

Other Investigators: *[list all site co-investigators, coordinators or study personnel]*

Participant's Printed Name:_____

This is a research study. Research studies include only people who want to take part. This form gives you information about this research, which will be discussed with you. It may contain words or procedures that you don't understand. Please ask questions about anything that is unclear to you. Discuss it with your family and friends and take your time to make your decision.

1. Purpose of the Research:

You are being offered the opportunity to take part in this research because you have a condition known as Polycystic Ovary Syndrome or PCOS. This condition is known to cause irregular periods, inability to get pregnant, and excessive facial and body hair.

The purpose of this study is to determine which of these two medications, Clomiphene Citrate (Clomid) or Letrozole (Femara), will most likely result in pregnancy and a live birth in women with PCOS. Clomiphene Citrate is a medication approved by the Food and Drug Administration (FDA) for ovulation induction or the releasing of an egg from your ovary to increase your chance of pregnancy. This medication is commonly used to achieve pregnancy in women with polycystic ovary syndrome. Letrozole (Femara) is an FDA approved medication for the treatment of breast cancer. This medication has been recently used in studies to induce ovulation but it is not yet FDA approved for this use.

Approximately 750 women will take part in this research among 7 nationwide sites. About *[insert site specific number]* women are expected to participate at the *[insert institution name]*.

2. Procedures to be Followed:

During your participation in this study, you will have a total of 12 visits to the *[insert institution name]*. You will begin with a screening visit to determine if you are eligible for study participation. Following screening you will have a baseline visit to receive your study medications. Following baseline, you will have a total of 5 monthly visits and an end of treatment visit.

Below is a brief chart explaining the visits and procedures to be completed for study. Following this chart, you will find explanations of the visits and EACH procedure in more detail.

Procedures	Screen	Baseline	Midluteal MV#1-5	Menses MV#1-4	End of Treatment
Sign Consent	X				
Complete questionnaires	X				X
Urine pregnancy test	X	X	X		X
Height & BMI	X				X
Weight	X	X	X		X
Vital signs	X	X	X		X
Hip & Waist measurements	X				X
Acne score	X				X
Sebumeter score	X		X		X
Hirsutism score	X				X
Blood work for male & female hormones	X				
Blood work for progesterone	X	X	X		X
Blood work for pregnancy	X	X	X	X	X
Blood work for Safety Labs	X				X
Blood work for study DNA		X			
Blood work for central core lab	X	X	X		X
Rubella, Varicella & HIV screen	X				
Blood work for repository		X			
Complete physical exam & pap smear	X				
Transvaginal ultrasound	X	X	X		X
Sonohysterogram or Hysterosalpingogram	X				
Semen Analysis	X				
Dispensed study meds		X	X		
Collect study meds			X		
Dispense daily journals		X	X		
Collect daily journals			X		X
Assess adverse events and concomitant meds			X		X

Before you have your first visit to the medical center, initial contact will be made either by email, telephone, or in clinic to determine if you qualify to take part in this research. A series of brief inclusion/exclusion eligibility questions will be asked to you. If you are eligible for this study you will be scheduled for a screening visit.

Screening Visit (Visit #1)- This visit will take approximately 2 hours to complete. You will report to the medical center after you have had nothing to eat or drink 10-12 hours prior to your visit. The following procedures will take place during this visit:

- This consent form will be reviewed by you and the study coordinator. You will have an opportunity to read this consent form in full and ask any questions you may have about the procedures involved, risks, and time commitments related to this study. Once all of your questions have been answered, you will sign this consent form. A copy will be provided to you for your records.
- Your past medical and menstrual history will be recorded. This form will ask a series of questions about your medical health, family health history, reproductive & gynecological history, pregnancy history, and the use of any medications you are currently taking.
- You will be given 6 questionnaires to complete. The PCOS Quality of Life (PCOS-QOL) will assess how PCOS affects your daily living. A female sexual function index (FSFI) and female sexual distress scale (FSDS) will assess your sexual function. A Medical Outcomes Survey (Prime MD-PHQ) and the Short Form-36 (SF-36) will assess your daily activities. FertiQol will assess how your infertility affects your thoughts and feelings. The Sleep Habits survey will assess your sleep habits. You will be free to skip any questions that you would prefer not to answer.
- A urine pregnancy test may be performed.
- Your height, weight, vital signs (including blood pressure, pulse, respirations, temperature), hip & waist measurements will be recorded.
- The amount of acne lesions on your face will be counted as well as measuring the oil on your forehead with a sebumeter will be performed.
- A hirsutism (excessive hair growth) assessment will be completed.
- A little more than 8 tablespoons of blood will be drawn to determine your eligibility for this study.

  -Male and female hormones such as total testosterone (Total T), sex hormone binding globulin (SHBG), and follicle stimulating hormone (FSH) will be assessed. Your Prolactin will be checked to make sure your body isn't producing too much. Your thyroid stimulating hormone (TSH) will be assessed to make sure your thyroid is functioning properly.

  -A 17-hyrdoxyprogesterone (17-OHP) will be checked for enzyme deficiency. If upon screening your 17-OHP is above the study criteria level, you will be asked to come back for a quick visit which will include having an ACTH stimulation test performed. The visit will involve having 1 teaspoon of blood drawn followed by an injection of Cortrosyn (0.25milligrams), which is a synthetic version of the hormone the brain secretes to control the adrenal gland. Cortrosyn is approved by the FDA for this use. One hour later another teaspoon of blood is removed and test is finished.

-A progesterone level will be performed to see if you are ovulating and a blood pregnancy test to make sure you are not pregnant.

-Blood work will also be evaluated to ensure that your kidneys and liver are functioning normally and that you are not anemic (safety labs).

-Blood will be collected and sent out to the Ligand Assay Core Lab at the University of Virginia for testing. Each site participating in this study will collect a blood sample at each visit from each participant to be tested by this central core lab for male & female hormone levels and glucose and insulin.

- You will have a complete physical exam including breast and pelvic exam performed by the physician. You will have a Pap smear done if you are twenty-one or older and have not had one done within the time period specified by current guidelines.
- A transvaginal ultrasound will be performed. This involves inserting an ultrasound probe into your vagina to visualize your ovaries and uterus. Measurements and ultrasound pictures will be recorded of your ovaries and uterus.
- At this time if you have not had a test within the past 3 years to determine that your fallopian tubes are open, a sonohysterogram or hysterosalpingogram will be completed. During the sonohysterogram, sterile saline fluid is injected through an intrauterine catheter that contains a balloon. The balloon is inflated and the shape of the uterus can be seen and the fluid that accumulates in the back area of your uterus determines that at least one fallopian tube is open. If it can't be determine that your fallopian tube is open during this procedure or the principal investigator sees it necessary to perform a different test, you may be required to have the hysterosalpingogram. This is done in the radiology department using a radioactive contrast dye that is injected and visualized flowing through the fallopian tube. If you have been pregnant within the last three years and your pregnancy and delivery were uncomplicated, the sonohysterogram or hysterosalpingogram may not be necessary.
- A semen analysis is required to determine a sperm concentration of greater than 14million/mL for entry into the study. Your partner/spouse will have to sign a Semen Analysis Consent Form and must provide a sample of his semen (if not already done with the past year) to assure that the sperm concentration is enough to meet the study criteria. If your partner/spouse has documentation within the past year of a semen analysis, he will be asked to sign a medical release form permitting the coordinator to obtain his semen analysis records. Your partner will also be asked to complete a medical history questionnaire and five quality of life questionnaires.
- You will be offered pre-conceptional counseling during this visit. Your family genetic history will be reviewed and any potential problems that may lead to complications during pregnancy will be addressed at this time. Additionally, you will be offered blood tests to determine if you are immune to Rubella (German Measles) or Varicella (not necessary if you have ever had chicken pox) or to see if you are infected with the HIV virus. If these tests are abnormal, you will be referred for appropriate treatment and counseling however, they will not prevent you from being eligible for this study. You will be given a prescription to take to your pharmacy for prenatal vitamins or folic acid which you will take daily throughout this study. A daily prenatal vitamin or 400mcg of folic acid has been found to

reduce certain types of birth defects. You will be instructed on healthy behaviors to follow while seeking pregnancy such as diet, exercise, and stopping smoking.

- At this visit, you will also be given a prescription to take to your pharmacy for medroxyprogesterone acetate (Provera). This medication is used to bring on a menstrual period. You will not start this medication until you have been determined eligible for further study participation. The study coordinator will instruct you on the use of this medication and when to start it after all your blood work and screening tests have been completed.
- You will be dispensed urine pregnancy tests to be used at home when instructed.

Randomization- When you have met all of the criteria for participation in this study, you will be randomized to the study medication. You will not need to be present at the medical center for this to occur. You will be randomized into a research group by a procedure similar to the toss of a coin. You will have a 50-50 chance of receiving either of the study drugs Clomiphene Citrate or Letrozole. Neither your study coordinator, physician, nor you, will know which study medication you are receiving. All of the pills will look identical. The coordinator will call you by phone and discuss your results and if necessary the start of Provera. If your progesterone result from the screening visit is non-ovulatory, and your pregnancy blood work is negative, and you have not had a recent menstrual period, you will take a 10-day course of Provera (5 mg pills) to bring on a menstrual period. You will take one pill each day and finish all the medication even if you start your menstrual cycle before you are finished with the dose. Take all of the medication. Once you start your menstrual cycle, call the study coordinator to schedule your baseline visit.

Baseline Visit (Visit #2)-You will come to the medical center fasting for this visit and it should last approximately 1 hour. This visit must occur sometime between days 1-5 of your menstrual cycle. The following procedures will take place at this visit:

- A urine pregnancy test may be performed at this visit.
- A brief physical exam including weight and vital signs will be recorded.
- A little more than 2 tablespoon of blood will be drawn to test your progesterone level, screen your blood for pregnancy, and blood will be sent to the central core lab. If you have consented for your blood to be collected for the repository, this will also be drawn at this time. If you also consented for your blood to be drawn for the study DNA collection, this will also be drawn at this time. This purpose of this DNA collection is to identify certain key genes (called polymorphisms) that may predict a response to the medications used in this trial.
- A transvaginal ultrasound will be performed.
- Your study medications will be dispensed to you at this time. You will receive a medication kit containing 3 medication bottles inside. In each of the bottles, you will receive either Clomiphene Citrate 50mg pills or Letrozole 2.5mg pills, with each bottle holding 5 pills. Every bottle will contain the same medication. You will be instructed on how to begin your medication. The study coordinator will call you within 24 hours as soon as your blood work results are available. If the results of your progesterone and pregnancy blood work are negative, you will begin your study medications. You will start with the first bottle in the kit and take 1 pill daily for 5 days. Once you have completed 5 days of medication, your first bottle

should be empty. You will NOT use the other study medication bottles for this cycle.
- Completion of any remaining questionnaires from the Screening Visit.
- You will be given daily journal logs to complete for each cycle. On these logs, you will record menstrual cycles, dates when you took your study medication, intercourse frequency, and side effects you have from the study medications. You will be instructed to have intercourse on a regular basis (at least 2 to 3 times per week separated by at least one day) to increase your chance of pregnancy. Intercourse that occurs too infrequently (less than once a week) or too frequently (more than once a day), may lower your chances for pregnancy. You will also keep a list of all medications such as over-the-counter, herbal, or vitamins you are taking.
- If you need more home pregnancy tests, they will be dispensed to you at this time.
- You will schedule your next visit.

Monthly Midluteal Visits (Visit #3,5,7,9,11)- You will follow-up monthly for a brief visit with the study coordinator and physician. These visits should last approximately 1 hour. You are required to be fasting for each of these visits. These monthly visits will take place during the midluteal phase of your menstrual cycle or approximately 3 weeks after you took your medication. The following procedures occur at each of these monthly visits:
- A urine pregnancy test will be done.
- A brief physical exam including weight, and vital signs will be recorded.
- A sebumeter assessment will be done to measure the amount of oil in your forehead.
- A little more than 2 tablespoons of blood will be drawn to test your progesterone level, screen your blood for pregnancy if necessary, and blood will be sent to the central core lab.
- A transvaginal ultrasound will be performed to assess your ovaries for the formation of any follicles and to determine if ovulation may occur.
- You will return your study medication kit and all the medication bottles to the study coordinator. A pill count will be performed to determine compliance with the study medications.
- You will return your daily journal logs for review by the study coordinator. A new set of daily journal logs will be provided to you for your next cycle.
- A new study medication kit will be dispensed to you for the next cycle, but you will not take any of the medication until you are told to do so by your study coordinator. (At Monthly Visit #5, you will not receive any study medications as you will be in the middle of your final cycle.)
- If you need more home pregnancy tests, they will be dispensed to you at this time.
- The study coordinator will call you within 24 hours with the results of your blood work. The study coordinator will discuss with you your progesterone result and if you have ovulated or not.

Monthly Menses Visits (Visit #4,6,8,10)- After 2 weeks from your midluteal visit or when you begin your period, you will be required to have a blood pregnancy test. This can

occur either at the medical center or at an outside laboratory or hospital in your area if that is more convenient. The study coordinator will call you as soon as the results are available. Directions for your next cycle dose will be reviewed with you at this time. One of the following will occur:

-If you have ovulated (a progesterone level of greater then 3ng/mL) during a cycle, you will wait for a menstrual cycle or a positive urine pregnancy test. If you start a menstrual cycle, you will begin your medication on day 3 or your menstrual period at the same dose you had the previous cycle and continue that for 5 days. You will continue at the same dose throughout the study as long as you are ovulating. You will continue this dose until pregnancy or until a total of five cycles or 25 weeks of study medication have been reached. If you have a positive pregnancy test, you will be scheduled for a termination visit and a transvaginal ultrasound will be performed to assess how the pregnancy is progressing.

-If you did not ovulate during a cycle, you will increase your medication to the next dose. You will begin at the next highest dose as instructed by the study coordinator. Once you have reached the highest dose of medication (3 pills once a day for 5 days), you will continue that dose for a total of 5 cycles or approximately 25 weeks or until you have a positive pregnancy test.

-If you have become pregnant, you will be scheduled for an end of treatment visit.

End of Treatment Visit (Visit #12)- This visit will occur at the end of the 5th cycle or after pregnancy has occurred, whichever happens first. You will be fasting for this visit and this visit should last approximately 1 hour.

- A complete physical exam will be performed including height, weight, vital signs and hip & waist measurements.
- A urine pregnancy test may be performed at this visit.
- Repeat acne lesion count, sebumeter, and hirsutism assessments will be completed.
- You will be asked to complete the PCOS-QOL, SF-36, Prime MD-PHQ, FSFI and FSDS questionnaires as you did at the screening visits
- Approximately 4 tablespoons of blood will be drawn to test your final progesterone level, screen your blood for pregnancy if necessary, and send blood to the central core lab. Your safety lab blood work will be repeated to ensure that your kidney and liver function haven't been affected by the study medication.
- You will return your final set of daily journal logs for review by the study coordinator.
- If you have become pregnant, you will have blood drawn to test your blood for your hCG level. This measures the amount of pregnancy hormone in your blood. You will have this test repeated approximately 48 hours after the first one. Once your hCG level has reached a high level, you will be scheduled for an obstetrical ultrasound. After your pregnancy has been determined to be proceeding normally, which will be around 6-8 weeks, you will follow up with your regular doctor for prenatal pregnancy care. If you do not have a doctor who delivers babies, you will be referred to one.

  Pregnancy care is not part of the study. Before being released from the study, you will be asked to sign a medical release form so the study coordinator can

obtain your pregnancy and delivery information. You will be instructed to contact the study coordinator throughout the pregnancy to report any pregnancy complications that may occur. The study coordinator will contact you by phone at approximately 12 weeks of pregnancy to find out if your pregnancy is still ongoing. Once you deliver, you will be contacted approximately 6 weeks later to find out the results of your labor, delivery, and infant information. At this time, we will also offer you the option of longer follow-up of your child to determine how your child develops.

3. Discomforts and Risks:

Below is a table listing all tests or procedures involved in this research and their related discomforts and risks.

Test or Procedure	Discomforts and Risks
Standard venipuncture for blood work	Slight pinch or pin prick, discomfort, black and blue mark at the site of puncture, small blood clot, infection or bleeding at the site, and fainting during the procedure
Transvaginal ultrasound	Abdominal or pelvic discomfort
Sonohysterogram or Hysterosalpingogram	Pain, bleeding, damage to the uterus, pelvic infection, interrupting an unrecognized pregnancy, small amount of radiation exposure, allergic reaction to the radioactive dye
Clomiphene Citrate	Visual changes (such as blurring of vision, double vision, floaters), abdominal pain, nausea, vomiting, constipation, mood changes, headache, hot flashes, fatigue, abnormal endometrial thickening, multiple pregnancies, formation of ovarian cyst, breast discomfort, abnormal uterine bleeding, and bloating
Letrozole	Fatigue, dizziness, nausea, hot flashes, arthritis pain in your joints, back pain, increased cholesterol levels, formation of ovarian cysts, multiple pregnancies
Medroxyprogesterone Acetate (Provera)	Nausea, breast tenderness, rash, skin sensitivity to the sun

It is not expected that patients will have all of these side effects. If you are feeling fatigue or dizziness associated with these medications, caution should be taken while driving or operating machinery.

Side effects are usually temporary and manageable. However, it is possible they could be more serious. In addition to the risks described above, there may be unknown risks we cannot predict while participating in this research. It is important that you notify your study coordinator if you experience any of these symptoms listed above and keep accurate documentation of these side effects on your daily journal logs. The investigators will let you know if they learn anything that might make you change your mind about participating in this research. You should check with your study doctor before starting any new prescription, over the counter medications, vitamins or herbal supplements.

Although these drugs may result in pregnancy, there is no guarantee that this will result in a live birth. Clomiphene has been associated with a 5% multiple pregnancy rate in women with PCOS. Multiple pregnancies are more likely to end early in preterm labor and are more likely to experience most pregnancy complications including diabetes and high blood pressure during pregnancy. The multiple pregnancy rates with Letrozole are unknown, but is probably more than the natural rate of 1% but less than Clomiphene Citrate.

You will be assigned to a treatment group by chance. The treatment you receive may prove to be less effective or to have more side effects than the other research treatments or other available treatments.

You will be given the option of having your blood tested for HIV. The results of this test could indicate that you are positive for HIV. If that happens, we will refer you to a doctor who specializes in managing HIV. We will make every effort to keep your personal information confidential.

You will be given pre-conceptional counseling for healthy behaviors in pregnancy throughout this study. You will be followed through study, after a positive pregnancy test, to confirm the location and viability of the pregnancy before being released to your Ob-Gyn physician. It is possible that your pregnancy may be nonviable or a pregnancy is detected in your fallopian tube and will require further medical or surgical treatment. You will have the option to follow up with your personal physician or be followed with us and with your permission, notify your physician regarding abnormalities.

Finally, the use of these drugs may be associated with an increased risk of harm to the embryo or fetus or fetal malformations during development, though no specific pattern has been associated with either drug. You will be instructed to immediately stop all study medications once you have a positive pregnancy test. You will not be taking the study medication during your pregnancy although the study drug may still be in your blood system and lead to harmful effects on the developing fetus.

There is a risk of loss of confidentiality if your medical information or your identity are obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

4. Possible Benefits:

a. Possible benefits to the participant:

The potential benefit to you is that the treatment you receive may prove to be more effective than the other study drug treatment or other available treatments, and you may become pregnant, although this cannot be guaranteed.

With the results of your hormone testing, you may have a greater understanding of the cause of your anovulation and infertility.

Abnormalities such as ovarian cysts or abnormalities of the uterine lining may be noted on ultrasound. You may have the benefit of restored ovulation and normal menstrual cycles which may lead to a successful pregnancy.

There is no guarantee that you will benefit from being in this research.

b. Possible benefits to others:

The knowledge gained in this research is important for establishing not only effective ovulation therapies for women with PCOS and infertility but also a better understanding and possibly treating later pregnancy complications. This study will also hold important information for the treatment of PCOS women not seeking pregnancy. The knowledge gained in this research may help discover the best and safest way to achieve pregnancy in women with polycystic ovary syndrome and which medication will be best used to achieve that goal of a pregnancy with a live birth.

5. Other Options that Could be Used Instead of this Research:

You may elect not to participate in this research study. If you decline to participate in this study, it will not affect any care or treatment you would normally receive from your regular doctor. You can talk with your doctor about other therapies for causing ovulation in polycystic ovary syndrome. Clomiphene Citrate is available to you without taking part in this research study.

6. Time Duration of the Procedures and Study:

If you agree to take part in this study, your involvement could last approximately 24 weeks. It will take about 4 weeks to go through the screening process and await your blood test results to determine your eligibility. Once you receive your study medications, you will be on them for about 25 weeks or 5 cycles. Below is a time table that lists the visits and their time lengths:

Visits	Length of Time
Screening (Visit #1)	2 hours
Baseline (Visit #2)	1 hour
Monthly Midluteal Visits (Visit #3,5,7,9,11)	1 hour
Monthly Menses Visits (Visit #4,6,8,10)	5 minutes
Termination (Visit #12)	1 hour

If you become pregnant, you will be contacted by the study coordinator throughout your pregnancy to obtain information regarding complications and status of the pregnancy. Within 6 weeks of the delivery of your baby, you will be contacted by the study coordinator to obtain all the delivery information. This would be a total time of 9 months of pregnancy and 6 weeks post delivery.

7. Statement of Confidentiality:

a. Privacy and confidentiality measures:

Your records that are used in the research at *[insert institution name]* will include your study identification number, your initials, and visit date and will be kept in a secured area in a locked file cabinet. Your samples collected for research purposes will be labeled

with your study identification number, initials, and visit date and will be stored in a -80 freezer in a locked laboratory and the list linking your sample to your identification will be kept in a password-protected computer file. Only the investigators involved in this research will have access to the list.

For research records sent to the Data Coordination Center at Yale University, you will be identified by your study identification number and study visit date. For specimens sent to the Ligand Assay Core Lab at the University of Virginia or study DNA samples sent to the University of Pennsylvania, you will be identified by study identification number, type of study visit, and visit date. The list that matches your name with your code number will be kept in a secured area in a locked file cabinet. If you consent to participate in the central repository blood collection, your specimen will be identified by a barcode label, study ID, sample type and the date of draw. Your specimen will not identify you and you cannot be linked to your specimen.

To help protect your privacy, a Certificate of Confidentiality was obtained from the federal government. This Certificate means that the researchers cannot be forced (for example by court subpoena) to share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the U.S. government that is used for checking or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate, however, does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. This means that you and your family should actively protect your own privacy.

You should know that we may provide information to your health care providers if we suspect that you may harm yourself or others. We will not release any information collected as part of the research regarding use of illicit drugs and testing for drugs done on samples collected for the research.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

b. The use of private health information:

If you give your consent, health information about you will be collected for this research. Health information is protected by law as explained in the *[insert institution name]* Privacy Notice. If you have not received this notice, please request a copy from the researcher. At *[insert institution name]* your information will only be used or shared as explained in this consent form or when required by law. However, some of the other

people/groups who receive your health information may not be required by Federal privacy laws to protect your information and may share it without your permission.

If you do not want us to use your protected health information, you may not participate in this research.

Your permission for the use, storage, and sharing of your identifiable health information will continue indefinitely. Any research information in your medical record will be kept indefinitely.

If you choose to participate, you are free to withdraw your permission for the use and sharing of your health information and your samples at any time. You must do this in writing. Write to *[insert name of principal investigator]* and let him know that you are withdrawing from the research study. His mailing address is:

[insert contact information of principal investigator]

If you withdraw your permission:

- We will no longer use or share medical information about you or your samples for this research study, except when the law allows us to do so.
- We are unable to take back anything we have already done or any information we have already shared with your permission.
- We may continue using your and sharing the information obtained prior to your withdrawal if it is necessary for the soundness of the overall research.
- We will keep our records of the care that we provided to you as long as the law requires.

The research team may use the following sources of health information.

-Personal health history
-Physical exam and pap smear results
-Blood sample results
-Transvaginal ultrasound results
-Urine sample results
-Sonohysterogram or Hysterosalpingogram results
-Questionnaires
-Medical history
-Menstrual and intercourse daily journal logs
-Pregnancy & Delivery information

Representatives of the following people/groups within *[insert institution name]* may use your health information and share it with other specific groups in connection with this research study.

- The principal investigator, *[insert name of principal investigator]*
- The *[insert institution name]* Institutional Review Board
- The *[insert institution name]* Human Subjects Protection Office
- The members of the research team working with *[insert name of principal investigator]*
- The study coordinators

The above people/groups may share your health information with the following people/groups outside *[insert institution name]* for their use in connection with this research study. These groups, while monitoring the research study, may also review and/or copy your original *[insert institution name]* records.

- The Office of Human Research Protections in the U.S. Department of Health and Human Services
- Food and Drug Administration
- Data Coordination Center at Yale University
- Reproductive Medicine Network of the The Eunice Kennedy Shriver National Institute of Child Health and Human Development
- University of Pennsylvania for DNA core facility
- National Institute of Health

8. Costs for Participation:

a. Costs:

The following is a list of all the covered services related to this study:
[insert site specific covered costs]

- Screening Visit including:
  -Hormone blood work
  -Pregnancy screening
  -Safety labs including liver and kidney functions & complete blood counts
  -Core, DNA, and repository blood work
  -Physical exam
  -Transvaginal ultrasound
  -Pap smear
- Each monthly visit including blood work & ultrasound
- Study medications including Clomiphene Citrate and Letrozole
- Termination visit blood work
- All pregnancy blood work
- 1st & 2nd OB ultrasounds

All of the above listed items will be provided at no cost to you. All study procedures once you have started the medication, if performed for the purpose of the study, will be paid for by the study. You will not incur any additional costs as a participant in this study.

The following is a list of the non-covered services related to this study:
[insert site specific non-covered costs]

- Rubella, Varicella, & HIV testing
- Hysterosalpingogram (HSG) or Sonohysterogram (SHG) based on the standard clinical practice at each site
- Provera and Folic Acid prescriptions
- Semen analysis
- Remaining OB ultrasounds

- Pregnancy care & delivery

You or your insurance carrier will be responsible for covering the costs of these tests. You or your insurance carrier will also be responsible for any blood test not related to this study, and any further testing or treatment related to preconceptional counseling.

b. Treatment and compensation for injury:

Every effort to prevent injury as a result of your participation will be taken. It is possible, however, that you could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. It is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury.

Costs for the treatment of research-related injuries will be charged to your insurance carrier or to you. Some insurance companies may not cover costs associated with research studies. If for any reason these costs are not covered by your insurance, they will be your responsibility. You will also be responsible for any deductible, co-insurance and/or co-pay.

You will not lose any legal rights by signing this form.

9. Compensation for Participation:

You will not receive any compensation for being in this research study.

10. Research Funding:

The institution and investigators are receiving a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Reproductive Medicine Network to support this research.

11. Voluntary Participation:

Taking part in this research study is voluntary. If you choose to take part in this research, your major responsibilities will include:

-compliance with study visits
-participation in all study related procedures
-participation in the collection of all blood work
-compliance with study medication regimen
-compliance with the documentation and collection of your menstrual and intercourse daily journal logs

You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide not to participate or if you decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which you are entitled.

Your research doctor may take you out of the research study without your permission. Some possible reasons for this are: you experience side effects and continuing the research study medications would be harmful to your health, or you did not follow the instructions of the study doctor. Also the sponsor of the research may end the research study early. If your participation in the research ends early, you may be asked to visit the research doctor for a final visit.

If you are participating in another clinical trial at *[insert institution name]* or elsewhere while in this research, you should discuss the procedures and/or treatments with your physician or the investigators. This precaution is intended to protect you from possible side effects from interactions of research drugs, treatments or testing.

During the course of the research you will be provided with any significant new findings that may affect your willingness to continue participating in this research.

12. Contact Information for Questions or Concerns:

You have the right to ask any questions you may have about this research. If you have questions, complaints or concerns or believe you may have developed an injury related to this research, contact *[insert name of principal investigator]* at xxx-xxx-xxxx or the Ob-Gyn resident doctor on 24-hour call at xxx-xxx-xxxx.

If you have questions regarding your rights as a research participant or you have concerns or general questions about the research or about your privacy and the use of your personal health information, contact the research protection advocate in the *[insert institution name]* Human Subjects Protection Office at xxx-xxx-xxxx. You may also call this number if you cannot reach the research team or wish to talk to someone else.

For more information about participation in a research study and about the Institutional Review Board (IRB), a group of people who review the research to protect your rights, please visit the *[insert institution name]* IRB's Web site at *[insert website address]*. Included on this web site, under the heading "Participant Info", you can access federal regulations and information about the protection of human research participants. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (xxx) xxx-xxxx.

Signature and Consent/Permission to be in the Research

Before making the decision regarding enrollment in this research you should have:

- Discussed this study with an investigator
- Reviewed the information in this form, and
- Had the opportunity to ask any questions you may have

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Participant: By signing this consent form, you indicate that you are voluntarily choosing to take part in this research.

_____	_____	_____	_____
Signature of Participant	Date	Time	Printed Name

Person Explaining the Research: Your signature below means that you have explained the research to the participant/participant representative and have answered any questions he/she has about the research.

_____ _____ _____ _____
Signature of person who explained this research Date Time Printed Name
(Only approved investigators for this research may explain the research and obtain informed consent.)

In addition to the main part of the research study, there are optional parts of the research. You can participate in the main part of the research without agreeing to take part in either of these optional parts.

Optional Study DNA Collection

As part of this study, we are obtaining, prior to you starting medication, a sample of your blood for DNA testing and for measure of other substances in the blood. If you agree, the researchers would like to use your DNA to identify certain sequences of key genes (called polymorphisms) that may predict a response to the medications used in this trial. If genes are identified, which are related to the response to the treatment, the sample may also be used in the development of diagnostic or prognostic tests to identify those who will or who will not respond to these medications. We also may use this DNA to identify genes that cause PCOS. There is no normal or abnormal result produced by the DNA and the researchers will not use the DNA to try to see if you have any genetic diseases or conditions. The testing of DNA may provide additional information that will be helpful in understanding the medications used in this trial and the effects on PCOS, but it is unlikely that these studies will have a direct benefit to you. The results of these tests will not have an effect on your care. Neither your doctor nor you will receive results of these tests, nor will the results be put in your health record. If you have any questions, you should contact *[insert name of principal investigator]* at xxx-xxx-xxxx.

If you agree to allow your DNA sample to be collected at the baseline visit, your DNA sample will be labeled with your study identification number and the visit date. These samples will be stored in a locked laboratory at the *[insert institution name].* After approximately 2 weeks of storage, your sample will be sent to a genetics laboratory for testing. You are free to change your mind regarding the use of your sample. You should contact *[insert name of principal investigator]* at xxx-xxx-xxxx and let him know you wish to withdraw your permission for your DNA to be used for testing. Your DNA sample will be destroyed at that time of withdrawal. You understand that you will not have access to the sample once it is sent to the laboratory. If you consent to the collection of your DNA, it will be kept indefinitely or until the sample is exhausted by the Reproductive Medicine Network.

You should initial below to indicate your preference for the collection of your DNA sample:

_____ I **give my permission** for my DNA and serum sample to be collected and tested under this study.

_____ I **decline my permission** for my DNA and serum sample to be collected for this study.

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____ _____ _____ _____
Signature of Participant Date Time Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions she has about the research.

_____ _____ _____ _____
Signature of person who explained this research Date Time Printed Name
(Only approved investigators for this research may explain the research and obtain informed consent.)

Optional Blood Repository Collection

As part of this study, we are obtaining a sample of your blood to be stored by the Reproductive Medicine Network for future use. If you agree, a little less than 2 tablespoons of your blood will be collected at the baseline visit and shipped to a central location and stored for a minimum of 5 years, and perhaps further into the future. Your sample will be tested for DNA and to measure other substances in your blood. The results of these tests will not have an effect on your care, and neither your doctor nor you will ever receive results of these tests. If you have any questions, you should contact *[insert name of principal investigator]* at xxx-xxx-xxxx.

If you agree to allow us to collect and store a blood sample from you for future use, your sample will be labeled with study ID, sample type, the date of the blood draw and a unique identifier, in the form of a barcode label. You will not be identified on your sample and your sample cannot be linked back to you. These samples will be stored in a locked laboratory at the *[insert institution name]* until shipment to the repository. Your blood samples may be shipped and stored in a biological specimen repository coordinated by the Reproductive Medicine Network pending approval by the Human Investigation Committees at all the participating sites. If you consent to the collection of your blood for the repository, it will be kept indefinitely or until the sample is exhausted by the Reproductive Medicine Network.

You should initial below to indicate your preference for the collection of your blood sample for the repository:

_____ I **give my permission** for my blood sample to be collected and sent to the repository for future testing.

_____ I **decline my permission** for my blood sample to be collected and sent to the repository for future testing.

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____	_____	_____	_____
Signature of Participant	Date	Time	Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions she has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Optional Blood Storage for Future Use

As part of this study, we are obtaining blood from you at each visit. If you agree, the researchers would like to store leftover samples of your blood so that your blood can be studied in the future after this study is over. These future studies may provide additional information that will be helpful in understanding polycystic ovary syndrome, but it is unlikely that these studies will have a direct benefit to you. The results of these tests will not have an effect on your care. Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record. Sometimes blood is used for genetic research about diseased that are passed on in families. Even if your samples are use for this kind of research, the results will not be put in your health records. It is possible that your blood might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur. If you have any questions, you should contact *[insert name of principal investigator* at xxx-xxx-xxxx.

Your leftover samples will be labeled with your study identification number, your initials and the visit date. These samples will be stored in a locked laboratory at the *[insert institution name]*. If you consent to the collection of samples of blood for future research, the period for the use of the samples is unknown. Your blood samples may be shipped and stored in a biological specimen repository coordinated by the Reproductive Medicine Network pending approval by the Human Investigation Committees at all the participating sites. If you agree to allow your blood to be kept for future research, you will be free to change your mind at any time. You should contact *[insert name of principal investigator]* at xxx-xxx-xxxx and let him know you wish to withdraw your permission for your blood to be used for future research. Any unused blood will be destroyed and not used for future research studies.

You should initial below to indicate your preferences regarding the optional storage of your leftover blood for future research studies.

a. Your sample(s) may be stored and used for future research studies to learn about, prevent, treat or cure polycystic ovary syndrome.
_____ Yes _____ No

b. Your sample(s) may be stored and use for research about other health problems.
_____ Yes _____ No

c. Your sample(s) may be shared with other investigators/groups without any identifying information.
_____ Yes _____ No

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____ _____ _____ _____
Signature of Participant Date Time Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions she has about the research.

_____ _____ _____ _____
Signature of person who explained this research Date Time Printed Name
(Only approved investigators for this research may explain the research and obtain informed consent.)

11 Appendix A: Risk Factors for Genetic Disorders

The following questions are designed to determine if you have an increased risk of having a baby with a genetic disorder. Sometimes genetic disorders occur even when there is no history of problems in your family. The following questions are related to you and your immediate family including mother, father, sister, brother, child, or grandparent. If you answer "yes" to any of the following questions and would like more information, please discuss this with your physician.

Questions	Yes	No	Unknown	N/A
1. If you conceive during this study, will you be 35 or older when your baby is due?				
2. If you are of Mediterranean or Asian descent, does anyone in your family have thalassemia? (a blood disorder that causes anemia)				
3. Is there a family history of neural tube defects?				
4. Have you had a child with a neural tube defect?				
5. Does anyone in your family have a history of congenital heart defects? (heart problems when they were born)				
6. Does anyone in your family have a history of Down Syndrome?				
7. Have you ever had a child with Down Syndrome?				
8. If you are of Eastern European Jewish or French Canadian descent, does anyone in your family have a history of Tay-Sachs disease? (a disorder of the central nervous system)				
9. If you are of Eastern European Jewish descent, does anyone in your family have a history of Canavan disease? (a disorder of the central nervous system that leads to blindness and muscle weakness)				
10. If you are of African American descent, is there any history of sickle cell trait? (a type of anemia)				
11. If you are of African American descent, is there any history of sickle cell disease? (a type of anemia)				
12. Do you or anyone in your family have a history of hemophilia? (a disorder that causes bleeding)				
13. Do you or anyone in your family have a history of muscular dystrophy? (a neuromuscular disorder)				
14. Do you or anyone in your family have a history of cystic fibrosis? (a disorder that causes thick mucous in the lungs and other organs)				
15. Do you or anyone in your family have a history of Huntington's disease? (a degenerative brain disease)				
16. Do you or anyone in your family have a history of alpha-1 antitrypsin deficiency? (lack of a liver protein)				
17. Do you or anyone in your family have a history of mental retardation?				
17a. If yes to question 17, was this person ever tested for fragile-x syndrome? (a condition which can cause mild to severe mental retardation)				
18. Do you or anyone in your family have a history of any other genetic disease, chromosomal disorder or birth defects?				
19. Do you have any metabolic disorders such as diabetes or phenylketonuria (PKU)? (a disorder which prevents the normal use of protein foods)				
20. Have you ever had 3 or more miscarriages in a row?				
21. Have you ever had a baby that was stillborn?				

Partner Family History

The following questions are designed to determine if you have an increased risk of having a baby with a genetic disorder. Sometimes genetic disorders occur even when there is no history of problems in your family. The following questions are related to you and your immediate family including mother, father, sister, brother, child, or grandparent. If you answer "yes" to any of the following questions and would like more information, please discuss this with your physician.

Questions	Yes	No	Unknown	N/A
1. If you are of Mediterranean or Asian descent, does anyone in your family have thalassemia? (a blood disorder that causes anemia)				
2. Is there a family history of neural tube defects?				
3. Have you had a child with a neural tube defect?				
4. Does anyone in your family have a history of congenital heart defects? (heart problems when they were born)				
5. Does anyone in your family have a history of Down Syndrome?				
6. Have you ever had a child with Down Syndrome?				
7. If you are of Eastern European Jewish or French Canadian descent, does anyone in your family have a history of Tay-Sachs disease? (a disorder of the central nervous system)				
8. If you are of Eastern European Jewish descent, does anyone in your family have a history of Canavan disease? (a disorder of the central nervous system that leads to blindness and muscle weakness)				
9. If you are of African American descent, is there any history of sickle cell trait? (a type of anemia)				
10. If you are of African American descent, is there any history of sickle cell disease? (a type of anemia)				
11. Do you or anyone in your family have a history of hemophilia? (a disorder that causes bleeding)				
12. Do you or anyone in your family have a history of muscular dystrophy? (a neuromuscular disorder)				
13. Do you or anyone in your family have a history of cystic fibrosis? (a disorder that causes thick mucous in the lungs and other organs)				
14. Do you or anyone in your family have a history of Huntington's disease? (a degenerative brain disease)				
15. Do you or anyone in your family have a history of alpha-1 antitrypsin deficiency? (lack of a liver protein)				
16. Do you or anyone in your family have a history of mental retardation?				
16a. If yes to question 16, was this person ever tested for fragile-x syndrome? (a condition which can cause mild to severe mental retardation)				
17. Do you or anyone in your family have a history of any other genetic disease, chromosomal disorder or birth defects?				
18. Do you have any metabolic disorders such as diabetes or phenylketonuria (PKU)? (a disorder which prevents the normal use of protein foods)				

12 APPENDIX B: Core Lab Instructions from UVA Center for Research in Reproduction

PHONE: (434) 982-3675
FAX: (434) 982-0701
EMAIL: LIGANDCORE@VIRGINIA.EDU

ASSAY	TOTAL TESTOSTERONE	SHBG	INSULIN	PROINSULIN	GLUCOSE
METHOD	IMMULITE	IMMULITE	IMMULITE	ELISA	OLYMPUS
SAMPLE TYPE	SERUM	SERUM	SERUM/ HEP. PLASMA	SERUM	SERUM
SAMPLE VOLUME	20 UL X2	10 UL X2	100 UL X2	50 UL X2	50 UL X2
MIN. DEAD VOLUME	100 UL	100 UL	250 UL	NA	NA

NA= NOT APPLICABLE

TOTAL SAMPLE VOLUME NEEDED TO ASSAY ALL TESTS = 1 ML OF SERUM

SAMPLE COLLECTION PROCEDURES:
Normal venipuncture procedures should be followed. Please collect enough blood in a red top tube to give you 1 ml of serum. Allow red top to clot at least 30 minutes before separating. Separate by centrifuging samples 10 minutes at 4ºC and 3000 RPMs. Aliquot serum samples into plastic screw cap 1.5 ml vials with O-rings and store at -20ºC to -70ºC until they can be analyzed.

SHIPPING INSTRUCTIONS:

1. Notify lab before shipping samples. (Do not ship for weekend delivery.)
2. Ship samples frozen in watertight receptacles on dry ice by Fed-Ex Priority Overnight. Please adhere to all rules regarding shipment of hazardous material from your institution.
3. Ship to the following address: **University of Virginia**
   Center for Research in Reproduction
   OMS Suhling Bldg., RM 6921 Hospital Drive
   Charlottesville, VA 22908
   Attn: Valerie Long

LABELING:
Please purchase the labeling material and print the labels according to the suggestion of the Core lab. Vendor information and sample labels can be found in the manual of operation.

DATA OUTPUT:

The data will be transferred to the DCC and emailed to the appropriate investigator at the completion of the study as an Excel document, which will include the following information:
Sample #
History #
Average Result
Mean
SD
CV%

13 APPENDIX C: DNA Collection and Shipping

DNA Sample Shipping Log

PPCOS II DNA Collection

- Obtain two 7ml purple tops (containing EDTA) tubes from each patient
- Store labeled tubes in 4^{o} C refrigerator until shipment
- Record on this log:
  - -Patient study number
  - -Date sample was obtained
  - -Total number of tubes for each patient
  - -Your initials
- Complete a new log for each shipment
- Photocopy log for your records and store in your regulatory binder
- Enclose log with each shipment
- Notify Kathy Ewens or Wendy Ankener prior to shipping at (215)898-3696
- Pack samples on ice packs and ship every 2 weeks by overnight carrier to:

  Kathy Ewens / Wendy Ankener
  Department of Genetics
  University of Pennsylvania School of Medicine
  Room 460, Clinical Research Bldg.
  415 Curie Blvd
  Philadelphia, PA 19010-6145
  Phone: 215-898-3696

Patient Study #	Date of Sample	# of DNA Tubes	Coordinator's Initials
__ __ __-__ __ __	__ __/__ __ __/__ __ __ __ Day Month Year		
__ __ __-__ __ __	__ __/__ __ __/__ __ __ __ Day Month Year		
__ __ __-__ __ __	__ __/__ __ __/__ __ __ __ Day Month Year		
__ __ __-__ __ __	__ __/__ __ __/__ __ __ __ Day Month Year		
__ __ __-__ __ __	__ __/__ __ __/__ __ __ __ Day Month Year		
__ __ __-__ __ __	__ __/__ __ __/__ __ __ __ Day Month Year		
__ __ __-__ __ __	__ __/__ __ __/__ __ __ __ Day Month Year		
__ __ __-__ __ __	__ __/__ __ __/__ __ __ __ Day Month Year		

Ship Date: __ __/__ __ __/__ __ __ __ **Site#**__ __ __
Name:__________________________ **Page** ___**of** ___
Phone #:__ __ __-__ __ __-__ __ __ __

14 Appendix D: List of common medications excluded or requiring wash-out period

PPCOS Excluded Medications

A patient will be excluded from study if they are taking any medication that should not be discontinued and this medication would affect reproductive function or metabolism, or would interact with either study medication.

Hormonal Medications Requiring 1 month wash-out:

Progestins (Oral or Cyclic)

- medroxyprogesterone acetate (Provera, Cycrin, Amen, Curretab)
- megestrol (Megase)
- norethindrone (Aygestin)
- progesterone gel (Crinone)
- Micronized progesterone (Prometrium)

Hormonal Medications Requiring 2 month Wash-Out Period:

GnRH Agonists/Antagonists

- Leuprolide (Lupron)
- nafarelin (Synarel)
- buserelin
- gosarelin (Zoladex)
- ganarelix (Antagon)
- cetrorelix (Cetrotide)

Gonadatropins

- Pergonal
- Repronex
- Follistim
- Gonal-F
- Fertinex
- Metrodin

Injectable Contraceptives

- medroxyprogesterone acetate (Depo Provera)

Oral Contraceptives

- Any Brand

Continuous Progestins (Not including cyclic)

- Any Brand

Other Medications Requiring 2 month Wash-out Period:

Somatostatin
- octreotide (Sandostatin)
- lanreaotide

Anti-Acne
- isotretinoin(Accutane)

Anti-androgens
- cyproterone (Cyprostat)
- spironolactone (Aldactone)
- flutamide (Eulexin)
- finasteride (Proscar, Propecia)

Anti-diabetic
- acarbose (Precose)
- Insulin
- *sulfonylureas*
- acetahexamide (Dymelor)
- chlorpropamide (Diabinese)
- tolazamide (Tolinase)
- tolbutamide (Orinase)
- glimepiride (Amaryl)
- glipizide (Glucotrol)
- glyburide (DiaBeta Micronase)
- *thiazolidinediones*
- rosiglitazone (Avandia)
- pioglitazone (Actos)

Biguanides
- metformin (Glucophage)
- Incretins : GLP-1 Analogues/DPP-IV inhibitors
- sitagliptin (Januvia)
- vidagliptin (Glavus)
- exenatide (Byetta)

Anti-obesity
- diazoxide (Proglycem)
- orlistat (Xenical)
- sibutramine (Meridia)
- diethylpropion (Tenuate)
- phendimetrazine (Bontril)
- phentermine (Adipex-P, Fastin, Ionamin)

Calcium Channel Blockers

diltiazem (Cardizem, Dilacor, Tiazac, Diltia-XL)
verapamil (Isoptin, Calan)
amlodipine (Norvase)
felodipine (Plendil)
isradipine (DynaCirc)
nicardipine (Cardene)
nifedipine (Procardia, Adalat)
nifsoldipine (Sular)

Angiotensin Converting Enzyme (ACE) Inhibitors

Prinivil (lisinopril)
Captoten (captropril)
Cozaar (losartan)
multiple others

Medications with potential longer washouts (Contact DCC)

Contraceptive Implants
Norplant (levonorgestrel implants)
Implanon

15 Appendix E: SF 36 Health Survey

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)
   - Excellent ☐
   - Very Good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)
   - Much better than one year ago ☐
   - Somewhat better now than one year ago ☐
   - About the same as one year ago ☐
   - Somewhat worse now than one year ago ☐
   - Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	(Please circle one number on each line.)	Yes	No
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	Yes	No
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

16 Appendix F: Female Sexual Function Index

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

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Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very high confidence
- ☐ High confidence
- ☐ Moderate confidence
- ☐ Low confidence
- ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

17 Appendix G: PCOS Quality of Life Questionnaire

Health Related Quality-of-Life Questionnaire For Women With PCOS

Subject Identifier: _____ Date:_____

INSTRUCTIONS: These questions ask about the affects of polycystic ovary syndrome on your everyday living. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential.

To what extent have you felt that growth of visible hair on your chin has been a problem for you during the last two weeks:

1. Growth of visible hair on your chin?
   - ☐1 A severe problem
   - ☐2 A major problem
   - ☐3 A moderate problem
   - ☐4 Some problem
   - ☐5 A little problem
   - ☐6 Hardly any problem
   - ☐7 No problem

During the past two weeks, how much of the time have you felt:

2. Depressed as a result of having PCOS?
   - ☐1 All of the time
   - ☐2 Most of the time
   - ☐3 A good bit of the time
   - ☐4 Some of the time
   - ☐5 A little of the time
   - ☐6 Hardly any of the time
   - ☐7 None of the time

3. Concerned about being overweight?
   - ☐1 All of the time
   - ☐2 Most of the time
   - ☐3 A good bit of the time
   - ☐4 Some of the time
   - ☐5 A little of the time
   - ☐6 Hardly any of the time
   - ☐7 None of the time

4. Easily tired?
   - ☐1 All of the time
   - ☐2 Most of the time
   - ☐3 A good bit of the time
   - ☐4 Some of the time
   - ☐5 A little of the time
   - ☐6 Hardly any of the time
   - ☐7 None of the time

5. Concerned with infertility problems?
   - ☐1 All of the time
   - ☐2 Most of the time
   - ☐3 A good bit of the time
   - ☐4 Some of the time
   - ☐5 A little of the time
   - ☐6 Hardly any of the time
   - ☐7 None of the time

6. Moody as a result of having PCOS?
   - ☐1 All of the time
   - ☐2 Most of the time
   - ☐3 A good bit of the time
   - ☐4 Some of the time
   - ☐5 A little of the time
   - ☐6 Hardly any of the time
   - ☐7 None of the time

In relation to your last menstruation, how much were the following issues a problem for you:

7. Headaches? ☐1 A severe problem ☐5 A little problem ☐2 A major problem ☐6 Hardly any problem ☐3 A moderate problem ☐7 No problem ☐4 Some problem
8. Irregular menstrual periods? ☐1 A severe problem ☐5 A little problem ☐2 A major problem ☐6 Hardly any problem ☐3 A moderate problem ☐7 No problem ☐4 Some problem

To what extent has growth of visible hair on your upper lip been a problem for you during the last two weeks:

9. Growth of visible hair on upper lip? ☐1 A severe problem ☐5 A little problem ☐2 A major problem ☐6 Hardly any problem ☐3 A moderate problem ☐7 No problem ☐4 Some problem

During the past two weeks, how much of the time have you:

10. Had trouble dealing with your weight? ☐1 All of the time ☐5 A little of the time ☐2 Most of the time ☐6 Hardly any of the time ☐3 A good bit of the time ☐7 None of the time ☐4 Some of the time
11. Had low self-esteem as a result of your PCOS? ☐1 All of the time ☐5 A little of the time ☐2 Most of the time ☐6 Hardly any of the time ☐3 A good bit of the time ☐7 None of the time ☐4 Some of the time
12. Felt frustration in trying to lose weight? ☐1 All of the time ☐5 A little of the time ☐2 Most of the time ☐6 Hardly any of the time ☐3 A good bit of the time ☐7 None of the time ☐4 Some of the time
13. Felt afraid of not being able to have children? ☐1 All of the time ☐5 A little of the time ☐2 Most of the time ☐6 Hardly any of the time ☐3 A good bit of the time ☐7 None of the time ☐4 Some of the time

14. Felt frightened of getting cancer?
- ☐1 All of the time
- ☐2 Most of the time
- ☐3 A good bit of the time
- ☐4 Some of the time
- ☐5 A little of the time
- ☐6 Hardly any of the time
- ☐7 None of the time

Over the last two weeks, to what extent have the following issues have been a problem for you:

15. Growth of visible hair on your face?
- ☐1 A severe problem
- ☐2 A major problem
- ☐3 A moderate problem
- ☐4 Some problem
- ☐5 A little problem
- ☐6 Hardly any problem
- ☐7 No problem

16. Embarrassment about excessive body hair?
- ☐1 A severe problem
- ☐2 A major problem
- ☐3 A moderate problem
- ☐4 Some problem
- ☐5 A little problem
- ☐6 Hardly any problem
- ☐7 No problem

During the past two weeks how much of the time have you been:

17. Worried about having PCOS?
- ☐1 All of the time
- ☐2 Most of the time
- ☐3 A good bit of the time
- ☐4 Some of the time
- ☐5 A little of the time
- ☐6 Hardly any of the time
- ☐7 None of the time

18. Self-conscious as a result of having PCOS?
- ☐1 All of the time
- ☐2 Most of the time
- ☐3 A good bit of the time
- ☐4 Some of the time
- ☐5 A little of the time
- ☐6 Hardly any of the time
- ☐7 None of the time

In relation to your last menstruation, how much are the following issues were a problem for you:

19. Abdominal bloating?
- ☐1 A severe problem
- ☐2 A major problem
- ☐3 A moderate problem
- ☐4 Some problem
- ☐5 A little problem
- ☐6 Hardly any problem
- ☐7 No problem

20. Late menstrual period?
- ☐1 A severe problem
- ☐2 A major problem
- ☐3 A moderate problem
- ☐4 Some problem
- ☐5 A little problem
- ☐6 Hardly any problem
- ☐7 No problem

21. Menstrual cramps?
- ☐1 A severe problem
- ☐2 A major problem
- ☐3 A moderate problem
- ☐4 Some problem
- ☐5 A little problem
- ☐6 Hardly any problem
- ☐7 No problem

How much of the time during the last two weeks did you:

22. Feel like you are not sexy because of being overweight?
- ☐1 All of the time
- ☐2 Most of the time
- ☐3 A good bit of the time
- ☐4 Some of the time
- ☐5 A little of the time
- ☐6 Hardly any of the time
- ☐7 None of the time

23. Feel a lack of control over the situation with PCOS?
- ☐1 All of the time
- ☐2 Most of the time
- ☐3 A good bit of the time
- ☐4 Some of the time
- ☐5 A little of the time
- ☐6 Hardly any of the time
- ☐7 None of the time

24. Have difficulties staying at your ideal weight?
- ☐1 All of the time
- ☐2 Most of the time
- ☐3 A good bit of the time
- ☐4 Some of the time
- ☐5 A little of the time
- ☐6 Hardly any of the time
- ☐7 None of the time

25. Feel sad because of infertility problems?
- ☐1 All of the time
- ☐2 Most of the time
- ☐3 A good bit of the time
- ☐4 Some of the time
- ☐5 A little of the time
- ☐6 Hardly any of the time
- ☐7 None of the time

To what extent has growth of visible body hair been a problem for you during the last two weeks:

26. Growth of visible body hair?
- ☐1 A severe problem
- ☐2 A major problem
- ☐3 A moderate problem
- ☐4 Some problem
- ☐5 A little problem
- ☐6 Hardly any problem
- ☐7 No problem

All of the above questions have been answered to the best of my knowledge.

Signature:_____ Date: _____

18 Appendix H: Prime MD PHQ

Patient Initials:__ __ __
Study ID #: __ __-__ __ __ __
Date of Visit:__ __/__ __/__ __ __ __
Month Day Year

Patient Health Questionnaire

This questionnaire is an important part of providing you with the best health care possible. Your answers will help in understanding problems that you may have. Please answer every question to the best of your ability unless you are requested to skip over a question.

DATE _____ NAME _____ AGE _____ SEX: Female Male

1. During the last 4 weeks, how much have you been bothered by any of the following problems?	Not bothered at all	Bothered a little	Bothered a lot
a. Stomach pain	[ ]	[ ]	[ ]
b. Back pain	[ ]	[ ]	[ ]
c. Pain in your arms, legs, or joints (knees, hips, etc.)	[ ]	[ ]	[ ]
d. Menstrual cramps or other problems with your periods	[ ]	[ ]	[ ]
e. Pain or problems during sexual intercourse	[ ]	[ ]	[ ]
f. Headaches	[ ]	[ ]	[ ]
g. Chest pain	[ ]	[ ]	[ ]
h. Dizziness	[ ]	[ ]	[ ]
i. Fainting spells	[ ]	[ ]	[ ]
j. Feeling your heart pound or race	[ ]	[ ]	[ ]
k. Shortness of breath	[ ]	[ ]	[ ]
l. Constipation, loose bowels, or diarrhea	[ ]	[ ]	[ ]
m. Nausea, gas, or indigestion	[ ]	[ ]	[ ]

2. Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
a. Little interest or pleasure in doing things	[ ]	[ ]	[ ]	[ ]
b. Feeling down, depressed, or hopeless	[ ]	[ ]	[ ]	[ ]
c. Trouble falling or staying asleep, or sleeping too much	[ ]	[ ]	[ ]	[ ]
d. Feeling tired or having little energy	[ ]	[ ]	[ ]	[ ]
e. Poor appetite or overeating	[ ]	[ ]	[ ]	[ ]
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	[ ]	[ ]	[ ]	[ ]
g. Trouble concentrating on things, such as reading the newspaper or watching television	[ ]	[ ]	[ ]	[ ]
h. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	[ ]	[ ]	[ ]	[ ]
i. Thoughts that you would be better off dead or of hurting yourself in some way	[ ]	[ ]	[ ]	[ ]

Patient Initials:__ __ __
Study ID#:__ __-__ __ __ __

3. Questions about anxiety.

	NO	YES
a. In the last 4 weeks, have you had an anxiety attack - suddenly feeling fear or panic?	[ ]	[ ]

If you checked "NO", go to question #5.

	NO	YES
b. Has this ever happened before?	[ ]	[ ]
c. Do some of these attacks come suddenly out of the blue - that is, in situations where you don't expect to be nervous or uncomfortable?	[ ]	[ ]
d. Do these attacks bother you a lot or are you worried about having another attack?	[ ]	[ ]

4. Think about your last bad anxiety attack.

	NO	YES
a. Were you short of breath?	[ ]	[ ]
b. Did your heart race, pound, or skip?	[ ]	[ ]
c. Did you have chest pain or pressure?	[ ]	[ ]
d. Did you sweat?	[ ]	[ ]
e. Did you feel as if you were choking?	[ ]	[ ]
f. Did you have hot flashes or chills?	[ ]	[ ]
g. Did you have nausea or an upset stomach, or the feeling that you were going to have diarrhea?	[ ]	[ ]
h. Did you feel dizzy, unsteady, or faint?	[ ]	[ ]
i. Did you have tingling or numbness in parts of your body?	[ ]	[ ]
j. Did you tremble or shake?	[ ]	[ ]
k. Were you afraid you were dying?	[ ]	[ ]

5. Over the last 4 weeks, how often have you been bothered by any of the following problems?	**Not at all**	**Several days**	**More than half the days**
a. Feeling nervous, anxious, on edge, or worrying a lot about different things	[ ]	[ ]	[ ]

If you checked "Not at all", go to question #6.

b. Feeling restless so that it is hard to sit still	[ ]	[ ]	[ ]
c. Getting tired very easily	[ ]	[ ]	[ ]
d. Muscle tension, aches, or soreness	[ ]	[ ]	[ ]
e. Trouble falling asleep or staying asleep	[ ]	[ ]	[ ]
f. Trouble concentrating on things, such as reading a book, watching TV	[ ]	[ ]	[ ]
g. Becoming easily annoyed or irritable	[ ]	[ ]	[ ]

Patient Initials:__ __ __
Study ID#: __ __-__ __ __ __

	NO	YES
6. Questions about eating.		
a. Do you often feel that you can't control what or how much you eat?	[ ]	[ ]
b. Do you often eat, within any 2-hour period, what most people would regard as an unusually large amount of food?	[ ]	[ ]

If you checked 'NO' to either #6a or #6b, go to question #9.

	NO	YES
c. Has this been as often, on average, as twice a week for the last 3 months?	[ ]	[ ]

7. In the last 3 months have you often done any of the following in order to avoid gaining weight?	NO	YES
a. Made yourself vomit?	[ ]	[ ]
b. Took more than twice the recommended dose of laxatives?	[ ]	[ ]
c. Fasted - not eaten anything at all for at least 24 hours?	[ ]	[ ]
d. Exercised for more than an hour specifically to avoid gaining weight after binge eating?	[ ]	[ ]

	NO	YES
8. If you checked 'YES' to any of these ways of avoiding gaining weight, were any as often, on average, as twice a week?	[ ]	[ ]

	NO	YES
9. Do you ever drink alcohol (including beer or wine)?	[ ]	[ ]

If you checked "NO" go to question #11.

10. Have any of the following happened to you more than once in the last 6 months?	NO	YES
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health	[ ]	[ ]
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities	[ ]	[ ]
c. You missed or were late for work, school, or other activities because you were drinking or hung over	[ ]	[ ]
d. You had a problem getting along with other people while you were drinking	[ ]	[ ]
e. You drove a car after having several drinks or after drinking too much	[ ]	[ ]

11. If you checked off any problems on this questionnaire, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
[ ]	[ ]	[ ]	[ ]

Patient Initials:__ __ __
Study ID#: __ __-__ __ __ __

12. During the last 4 weeks, how much have you been bothered by any of the following problems?	Not bothered at all	Bothered a little	Bothered a lot
a. Worrying about your health	[ ]	[ ]	[ ]
b. Your weight or how you look	[ ]	[ ]	[ ]
c. Little or no sexual desire or pleasure during sex	[ ]	[ ]	[ ]
d. Difficulties with husband/wife, partner/lover or boyfriend/girlfriend	[ ]	[ ]	[ ]
e. The stress of taking care of children, parents or other family members	[ ]	[ ]	[ ]
f. Stress at work or outside of the home or at school	[ ]	[ ]	[ ]
g. Financial problems or worries	[ ]	[ ]	[ ]
h. Having no one to turn to when you have a problem	[ ]	[ ]	[ ]
i. Something bad that happened recently	[ ]	[ ]	[ ]
j. Thinking or dreaming about something terrible that happened to you in the past - like your house being destroyed, a severe accident, being hit or assaulted, or being forced to commit a sexual act	[ ]	[ ]	[ ]

13. In the last year, have you been hit, slapped, kicked or otherwise physically hurt by someone, or has anyone forced you to have an unwanted sexual act?	NO	YES
	[ ]	[ ]

14. What is the most stressful thing in your life right now?

_____

_____

15. Are you taking any medicine for anxiety, depression or stress?	NO	YES
	[ ]	[ ]

16. FOR WOMEN ONLY: Questions about menstruation, pregnancy and childbirth.

a. Which best describes your menstrual periods?
___ Periods are unchanged
___ No periods because pregnant or recently gave birth
___ Periods have become irregular or changed in frequency, duration or amount
___ No periods for at least a year
___ Having periods because taking hormone replacement (estrogen) therapy or oral contraceptive

	NO	YES
b. During the week before your period starts, do you have a serious problem with your mood - like depression, anxiety, irritability anger or mood?	[ ]	[ ]
IF YES: Do these problems go away by the end of your period?	[ ]	[ ]
c. Have you given birth within the last 6 months?	[ ]	[ ]
d. Have you had a miscarriage within the last 6 months?	[ ]	[ ]
e. Are you having difficulty getting pregnant?	[ ]	[ ]

19 Appendix I: Female Sexual Distress Scale (FSDS-R)∧

FEMALE SEXUAL DISTRESS SCALE
(Revised-2005)

_____

INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST 7 DAYS INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: **Personal responsibility for your sexual problems.**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1. Distressed about your sex life	0	1	2	3	4
2. Unhappy about your sexual relationship	0	1	2	3	4
3. Guilty about sexual difficulties	0	1	2	3	4
4. Frustrated by your sexual problems	0	1	2	3	4
5. Stressed about sex	0	1	2	3	4
6. Inferior because of sexual problems	0	1	2	3	4
7. Worried about sex	0	1	2	3	4
8. Sexually inadequate	0	1	2	3	4
9. Regrets about your sexuality	0	1	2	3	4
10. Embarrassed about sexual problems	0	1	2	3	4
11. Dissatisfied with your sex life	0	1	2	3	4
12. Angry about your sex life	0	1	2	3	4
13. Bothered by low sexual desire	0	1	2	3	4

20 Appendix J: FertiQol

FertiQoL International

Fertility Quality of Life Questionnaire (2008)

For each question, kindly check (tick the box) for the response that most closely reflects how you think and feel. Relate your answers to your current thoughts and feelings. Some questions may relate to your private life, but they are necessary to adequately measure all aspects of your life.

Please complete the items marked with an asterisk (*) only if you have a partner.

	For each question, check the response that is closest to your current thoughts and feelings	Very Poor	Poor	Nor good nor poor	Good	Very Good
A	How would you rate your health?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	Very Dissatisfied	Dissatisfied	Neither Satisfied Nor Dissatisfied	Satisfied	Very Satisfied
B	Are you satisfied with your quality of life?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	Completely	A Great Deal	Moderately	Not Much	Not At All
Q1	Are your attention and concentration impaired by thoughts of infertility?	☐	☐	☐	☐	☐
Q2	Do you think you cannot move ahead with other life goals and plans because of fertility problems?	☐	☐	☐	☐	☐
Q3	Do you feel drained or worn out because of fertility problems?	☐	☐	☐	☐	☐
Q4	Do you feel able to cope with your fertility problems?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	Very Dissatisfied	Dissatisfied	Neither Satisfied Nor Dissatisfied	Satisfied	Very Satisfied
Q5	Are you satisfied with the support you receive from friends with regard to your fertility problems?	☐	☐	☐	☐	☐
*Q6	Are you satisfied with your sexual relationship even though you have fertility problems?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	Always	Very Often	Quite Often	Seldom	Never
Q7	Do your fertility problems cause feelings of jealousy and resentment?	☐	☐	☐	☐	☐
Q8	Do you experience grief and/or feelings of loss about not being able to have a child (or more children)?	☐	☐	☐	☐	☐
Q9	Do you fluctuate between hope and despair because of fertility problems?	☐	☐	☐	☐	☐
Q10	Are you socially isolated because of fertility problems?	☐	☐	☐	☐	☐
*Q11	Are you and your partner affectionate with each other even though you have fertility problems?	☐	☐	☐	☐	☐
Q12	Do your fertility problems interfere with your day-to-day work or obligations?	☐	☐	☐	☐	☐
Q13	Do you feel uncomfortable attending social situations like holidays and celebrations because of your fertility problems?	☐	☐	☐	☐	☐
Q14	Do you feel your family can understand what you are going through?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	An Extreme Amount	Very Much	A Moderate Amount	A Little	Not At All
*Q15	Have fertility problems strengthened your commitment to your partner?	☐	☐	☐	☐	☐
Q16	Do you feel sad and depressed about your fertility problems?	☐	☐	☐	☐	☐
Q17	Do your fertility problems make you inferior to people with children?	☐	☐	☐	☐	☐
Q18	Are you bothered by fatigue because of fertility problems?	☐	☐	☐	☐	☐
*Q19	Have fertility problems had a negative impact on your relationship with your partner?	☐	☐	☐	☐	☐
*Q20	Do you find it difficult to talk to your partner about your feelings related to infertility?	☐	☐	☐	☐	☐
*Q21	Are you content with your relationship even though you have fertility problems?	☐	☐	☐	☐	☐
Q22	Do you feel social pressure on you to have (or have more) children?	☐	☐	☐	☐	☐
Q23	Do your fertility problems make you angry?	☐	☐	☐	☐	☐
Q24	Do you feel pain and physical discomfort because of your fertility problems?	☐	☐	☐	☐	☐

21 Appendix K: Sleep Habits Questionnaire

SLEEP HEART HEALTH STUDY

SLEEP HABITS QUESTIONNAIRE

ID#:

Field Center: ____ ____

Today's date: ____ ____ ____
month day year

Please complete as thoroughly as possible and to the best of your knowledge.

1 A. At what time do you usually FALL ASLEEP on weekdays or your work days?

____ ____ : ____ ____ ☐ 1 A.M. *(Midnight is 12:00 A.M.)* ☐ 2 P.M.

B. At what time do you usually FALL ASLEEP on weekends or your non-work days?

____ ____ : ____ ____ ☐ 1 A.M. *(Midnight is 12:00 A.M.)* ☐ 2 P.M.

2 How many minutes does it usually take you to fall asleep at bedtime?

____ ____ ____ *(Number of minutes)*

3 A. At what time do you usually WAKE UP on weekdays or your work days?

____ ____ : ____ ____ ☐ 1 A.M. ☐ 2 P.M.

B. At what time do you usually WAKE UP on weekends or your non-work days?

____ ____ : ____ ____ ☐ 1 A.M. ☐ 2 P.M.

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4 How many hours of sleep do you usually get at night (or your main sleep period) on weekdays or workdays?

____ ____ *(Number of hours)*

5 How many hours of sleep do you usually get at night (or your main sleep period) on weekends or your non-work days?

____ ____ *(Number of hours)*

6 During a usual week, how many times do you nap for 5 minutes or more? *(Write in "0" if you do not take any naps.)*

____ ____ *(Number of times)*

7 Please indicate how often you experience each of the following. *(Check one box for each item.)*

	NEVER (0)	RARELY (1/month or less)	SOMETIMES (2-4/month)	OFTEN (5-15/month)	ALMOST ALWAYS (16-30/month)
A. Have trouble falling asleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
B. Wake up during the night and have difficulty getting back to sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
C. Wake up too early in the morning and be unable to get back to sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
D. Feel unrested during the day, no matter how many hours of sleep you had.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
E. Feel excessively (overly) sleepy during the day.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
F. Do not get enough sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
G. Take sleeping pills or other medication to help you sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Questions 8 through 16 are about snoring and breathing during sleep. To answer these questions, please consider both what others have told you AND what you know about yourself.

8 Have you ever snored (now or at any time in the past)?

☐ 1 YES

☐ 0 NO → *Skip to Question 14 on page 4.*

☐ 8 DON'T KNOW → *Skip to Question 14 on page 4.*

9 How often do you snore now? *(Check one.)*

☐ 0 Do not snore any more. → *Skip to Question 13 on page 4.*

☐ 1 Rarely - less than one night a week.

☐ 2 Sometimes - 1 or 2 nights a week.

☐ 3 Frequently - 3 to 5 nights a week.

☐ 4 Always or almost always - 6 or 7 nights a week.

☐ 8 Don't know.

10 How loud is your snoring? *(Check one.)*

☐ 1 Only slightly louder than heavy breathing.

☐ 2 About as loud as mumbling or talking.

☐ 3 Louder than talking.

☐ 4 Extremely loud - can be heard through a closed door.

☐ 8 Don't know.

11 For how many years have you been snoring?

____ ____ *(Number of years)* **OR** Don't know ☐ 88

12 Is your snoring: ***(Check one.)***

- ☐ 1 Increasing over time?
- ☐ 2 Decreasing over time?
- ☐ 3 Staying the same?
- ☐ 8 Don't know.

13 Have you ever had surgery as treatment for your snoring?

☐ 1 YES ☐ 0 NO

14 Are there times when you stop breathing during your sleep?

☐ 1 YES ☐ 0 NO → *Skip to Question 16 on page 5.*

☐ 8 DON'T KNOW

15 How often do you have times when you stop breathing during your sleep?

- ☐ 1 Rarely - less than one night a week.
- ☐ 2 Sometimes - 1 or 2 nights a week.
- ☐ 3 Frequently - 3 to 5 nights a week.
- ☐ 4 Always or almost always - 6 or 7 nights a week.
- ☐ 8 Don't know.

16 A. Have you ever been told by a doctor that you had sleep apnea (a condition in which breathing stops briefly during sleep)?

☐ 1 YES ☐ 0 NO → *Skip to Question 17 below.*

☐ 8 DON'T KNOW → *Skip to Question 17 below.*

B. Do you sleep with either a pressure mask ("CPAP") or a mouthpiece as treatment for your sleep apnea?

☐ 1 YES ☐ 0 NO

C. Have you had surgery as treatment for your sleep apnea?

☐ 1 YES ☐ 0 NO

17 Do you usually use oxygen therapy (oxygen delivered by a mask or nasal cannula) during your sleep?

☐ 1 YES ☐ 0 NO

18 In the past year, how often, on average, have you been awakened with the following?

	NEVER (0)	RARELY (1/month or less)	SOMETIMES (2-4/month)	OFTEN (5-15/month)	ALMOST ALWAYS (16-30/month)
A. Coughing or wheezing.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
B. Chest pain or tightness.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
C. Shortness of breath.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
D. Sweats or hot flashes.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
E. Noise in your surroundings.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
F. Pain in your joints, muscles, or back.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
G. Heartburn or indigestion.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
H. Leg cramps or leg jerks.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I. Need to go to the bathroom.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

19 During the past year, how often have one or more members of your household been in or near the room where you have slept?

☐ 1 NEVER ☐ 2 SOMETIMES ☐ 3 USUALLY

20 What is the chance that you would doze off or fall asleep (not just "feel tired") in each of the following situations? *(Check one box for each situation. If you are never or rarely in the situation, please give your best guess for that situation.*

	NO CHANCE	SLIGHT CHANCE	MODERATE CHANCE	HIGH CHANCE
A. Sitting and reading.	☐ 1	☐ 2	☐ 3	☐ 4
B. Watching TV.	☐ 1	☐ 2	☐ 3	☐ 4
C. Sitting inactive in a public place (such as a theater or a meeting).	☐ 1	☐ 2	☐ 3	☐ 4
D. Riding as a passenger in a car for an hour without a break.	☐ 1	☐ 2	☐ 3	☐ 4
E. Lying down to rest in the afternoon when circumstances permit.	☐ 1	☐ 2	☐ 3	☐ 4
F. Sitting and talking to someone.	☐ 1	☐ 2	☐ 3	☐ 4
G. Sitting quietly after a lunch without alcohol.	☐ 1	☐ 2	☐ 3	☐ 4
H. In a car, while stopped for a few minutes in traffic.	☐ 1	☐ 2	☐ 3	☐ 4
I. At the dinner table.	☐ 1	☐ 2	☐ 3	☐ 4
J. While driving.	☐ 1	☐ 2	☐ 3	☐ 4

Field Center Use Only

☐ 0 Self administered

Interviewer administered, in:

☐ 1 English ☐ 4 Pima

☐ 2 Spanish ☐ 5 Other, specify:_____

☐ 3 Lakota ☐ 6 Unknown

Interviewer or Reviewer _____ _____ _____ Date: _____ _____ _____
month day year

22 Appendix L: International Index of Erectile Function (IIEF) Questionnaire

(Write the number that best describes your erectile function for the past 4 weeks in the spaces provided.)

Over the past four weeks: 1. How often were you able to get an erection during sexual activity? _____	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration? _____	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? _____	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
4. During intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? _____	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? _____	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
6. How many times have you attempted sexual intercourse? _____	0 = No attempts 1 = One to two attempts 2 = Three to four attmepts 3 = Five to six attempts 4 = Seven to ten attempts 5 = Eleven or more attempts
7. When you attempted sexual intercourse, how often was it satisfactory for you? _____	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always

8. How much have you enjoyed sexual intercourse? _____	0 = No intercourse 1 = No enjoyment 2 = Not very enjoyable 3 = Fairly enjoyable 4 = Highy enjoyable 5 = Very highly enjoyable
9. When you had sexual stimulation or intercourse, how often did you ejaculate? _____	0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax? _____	0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
11. How often have you felt sexual desire? _____	1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
12. How would you rate your sexual desire? _____	1 = Very low/none at all 2 = Low 3 = Moderate 4 = High 5 = Very high
13. How satisfied have you been with your overall sex life? _____	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
14. How satisfied have you been with your sexual relationship with your partner? _____	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
15. How would you rate your confidence that you could get and keep an erection? _____	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

*RC Rosen, A Riley, G Wagner et al. The international index of erectile dysfunction (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997 49: 822-30.

23 Appendix M: Patient Daily Journal

Patient Daily Journal Instructions
Source Document
Reproductive Medicine Network

Introduction

Welcome to the Pregnancy in Polycystic Ovary Syndrome (PPCOSII) research study. Your participation and interest in this study are very important. The purpose of this Patient Brochure and Daily Journal is to provide the following:

- General overview about research studies
- Specific information about PPCOS II research study
- Guidance in recording daily information during your participation in the study

Overview of a Research Study

A research study, also called a clinical trial, is an organized approach to finding new and better ways to treat or prevent health conditions. Advances in medicine come from new ideas and procedures developed through research. These ideas and procedures are then tested in research studies to show that they are safe and effective in a certain number of patients before they can become standard prescribed treatments.

Through research studies, investigators learn which treatments are more helpful than others. Today's most beneficial treatments were first shown to be effective in research studies.

PPCOS II Research Study

This research study will evaluate the effectiveness of 2 different types of medications to induce ovulation in infertile women with polycystic ovary syndrome. There will be about 750 women enrolled from different parts of the United States. You will be randomized, similar to flipping a coin, to either a treatment of Clomiphene Citrate or Letrozole.

The medication treatment period will last for either a maximum of 20 weeks (5 months) or until you become pregnant, whichever comes first. You will be seen monthly by the study staff during the time you are taking the study medication to undergo monthly blood tests and ultrasound examinations. These monthly study visits will include the following:

- Blood tests
- Transvaginal ultrasound
- Physical measurements
- Review of current medications
- Review of any symptoms you are having
- A pill count of your study medications
- Review of the information you enter in the journal

If you become pregnant, the study staff will contact you after your due date to determine the outcome of your pregnancy.

Progestins
Common side effects:
- Dizziness
- Headache
- Fatigue
- Depression
- Nausea
- Vomiting
- Decreased appetite
- Breakthrough bleeding
- Itchy rash
- Sun sensitivity-use sunscreen and wear protective clothing

Prior to Beginning Study Medications

Progestin
After your initial study visit, depending on the results of blood tests, you may be instructed to take a medication that will bring about a menstrual period. A common brand name of this medication is Provera. Progestin (5mg table) is taken once a day for 10 days. Your study coordinator will inform you when to begin the progestin.

Your period may start while you are still taking the progestin or may not start until 2 weeks after you finish the tablets. This is not unusual and you should still complete the 10 days of tablets, regardless of when your period starts. If you have not started a period and it has been 2 weeks since finishing the tablets, you should call your study coordinator and have a pregnancy test. If the pregnancy test is negative, you will be instructed to begin study medications.

Study Medications

Study Medication Tips:
- Take your medication with food or milk.
- Take your medication at the same time each day.
- Take your medication as prescribed and do not take more than your prescribed dose.
- Extra tablets are provided.
- Missed dose- take it as soon as you remember, please note the exceptions to this below:

  Progestin
  -If it almost time for our next dose, skip the missed dose, and resume your normal schedule.
  -Do not take double doses.

  Clomiphene Citrate/Letrozole
  -If it is almost time for your next dose, take both tablets at the same time, and resume your normal schedule.
  -If you miss more than two doses, contact your study coordinator.

- Record all doses you take and symptoms you have in the daily journal section.
- Record other medications you are taking including prescription, over-the-counter, and herbal products in the back of this journal.
- Bring all study medications containers (even empty ones) to each monthly study visit.
- Keep all medications out of reach of children.

Clomiphene Citrate or Letrozole

On cycle day 3 (the third day of full bleeding), you will begin to take clomiphene citrate or letrozole from the bottle in your study medication kit. You will take one tablet, at the same time each day, for 5 consecutive days. Do not take for more than five days in a row or take more than one tablet per day unless you are given specific instructions by your study coordinator to do so. Your physician may increase the dose of clomiphene citrate or letrozole up to 3 tablets a day based on the results of your blood tests.

Clomiphene Citrate or Letrozole Instructions		
Cycle Day 3	1 tablet	The dose may increase with each cycle depending on the results of your blood tests. It will never be more than 3 tablets each day.
Cycle Day 4	1 tablet	
Cycle Day 5	1 tablet	
Cycle Day 6	1 tablet	
Cycle Day 7	1 tablet	

Notify your physician or study coordinator immediately if you experience any of the following:

- Visual changes, including double or blurry vision
- Sudden weight gain (>5lbs. in 2 days)
- Severe abdominal bloating and pain
- Nausea or vomiting
- Decreased urination
- Dark colored urine

Clomiphene Citrate- Common Side Effects

-Hot flashes -Vomitting
-Mood changes -Constipation
-Headache -Rash
-Abdominal bloating and pain around time of ovulation
(4-10 days after completing study medication dose)

Letrozole- Common Side Effects

- Upset stomach -Hot flashes
-Back pain -Fatigue
-Arthritic pain in your joints

Adverse Events

Adverse events are any new symptoms, changes in current symptoms, or side effects that you experience while taking the study medication. You should record all of these on your daily journal in the comment's section and include the following information:

- Date side effect or symptom started
- Side effect or symptom you are having
- Intensity
  Mild: you are aware of it but it does not bother you
  Moderate: it is uncomfortable and may interfere with your daily activities
  Severe: it definitely interferes with your daily activities and requires contacting your study coordinator or physician
- Date side effect or symptom ends

Prenatal Vitamins

At the beginning of the study, you will be given a prescription for prenatal vitamins or folic acid (folate). Either one of these will provide the minimum recommended dose of folic acid to help prevent some birth defects. You should take one tablet daily during the study and continue through your pregnancy, if you become pregnant.

Healthy Living

Smoking has been shown to contribute to infertility, cause low infant birth weights, and to increase your risk of pregnancy complications, heart attacks, and other illnesses. Ask your primary care doctor about smoking cessation programs in your area.

Exercise and remaining active is important for all individuals. Talk to your primary care doctor before starting or increasing any exercise program. There are many activities that can give you the exercise you need such as walking, swimming, or riding a stationary bike. Exercise will help you feel better and may help prevent other health problems in the future by:

- Improving your stamina and quality of life
- Strengthening your heart and other muscles
- Improving your blood circulation

Healthy food habits can help reduce the risk factors and health problems such as heart attack, high blood pressure, high cholesterol, and excess body weight. Making changes in your eating patterns can have positive benefits for you. A healthy eating pattern includes consuming a variety of fruits, vegetables, grains, low-fat dairy products, fish, legumes, and lean meats.

Patient Daily Journal
Source Document
Reproductive Medicine Network

Patient Initials:__ __ __
Study ID #:__ __ __ -__ __ __
Corresponding Visit:_____

Day	Date	Cycle Day	# of Tablets Taken	IC	Bleeding Bleeding=blood loss requiring use of sanitary protection Spotting=blood loss not necessitating sanitary protection	Did you experience any side effects from the study medication?	Concomitant Medications
Monday	___/___/___	___	___ AM ___ PM	☐ Yes ☐ No	☐ None ☐ Spotting ☐ Bleeding	☐ Yes → Record below under corresponding day ☐ No	☐ Yes → Record below under corresponding day ☐ No
Tuesday	___/___/___	___	___ AM ___ PM	☐ Yes ☐ No	☐ None ☐ Spotting ☐ Bleeding	☐ Yes → Record below under corresponding day ☐ No	☐ Yes → Record below under corresponding day ☐ No
Wednesday	___/___/___	___	___ AM ___ PM	☐ Yes ☐ No	☐ None ☐ Spotting ☐ Bleeding	☐ Yes → Record below under corresponding day ☐ No	☐ Yes → Record below under corresponding day ☐ No
Thursday	___/___/___	___	___ AM ___ PM	☐ Yes ☐ No	☐ None ☐ Spotting ☐ Bleeding	☐ Yes → Record below under corresponding day ☐ No	☐ Yes → Record below under corresponding day ☐ No
Friday	___/___/___	___	___ AM ___ PM	☐ Yes ☐ No	☐ None ☐ Spotting ☐ Bleeding	☐ Yes → Record below under corresponding day ☐ No	☐ Yes → Record below under corresponding day ☐ No
Saturday	___/___/___	___	___ AM ___ PM	☐ Yes ☐ No	☐ None ☐ Spotting ☐ Bleeding	☐ Yes → Record below under corresponding day ☐ No	☐ Yes → Record below under corresponding day ☐ No
Sunday	___/___/___	___	___ AM ___ PM	☐ Yes ☐ No	☐ None ☐ Spotting ☐ Bleeding	☐ Yes → Record below under corresponding day ☐ No	☐ Yes → Record below under corresponding day ☐ No

Day	Date	Side Effects/Comments Mild= does not affect your daily activity Moderate=requires a change to your daily activity Severe= requires a phone call to your doctor	Concomitant Medications Record name of drug, dose/strength, and time you took the medication
Monday	___/___/___		
Tuesday	___/___/___		
Wednesday	___/___/___		
Thursday	___/___/___		
Friday	___/___/___		
Saturday	___/___/___		
Sunday	___/___/___		

24 Appendix N: Sample Male Consent Form

CONSENT FOR RESEARCH

Title of Project: Pregnancy in Polycystic Ovary Syndrome II (PPCOS II):
A 25-week, Double-Blinded, Randomized Trial of Clomiphene Citrate and Letrozole for the Treatment of Infertility in Women with Polycystic Ovary Syndrome

Male Partner Consent Form

Principal Investigator: *[insert site principal investigator name]*

Other Investigators: *[insert site co-investigators, study coordinators, and study personnel]*

Participant's Printed Name:_____

This is a research study. Research studies include only people who want to take part. This form gives you information about this research, which will be discussed with you. It may contain words or procedures that you don't understand. Please ask questions about anything that is unclear to you. Discuss it with your family and friends and take your time to make your decision.

1. Purpose of the Research:

The purpose of this research is to determine if your partner/spouse are eligible to participate in the study for polycystic ovary syndrome and pregnancy. As part of standard care for an infertility work-up, a semen analysis is required from the partner or spouse. A sperm concentration of greater than 14 million/mL will determine eligibility.

2. Procedures to be Followed:

During the screening visit for your partner/spouse, you will receive this consent form with all the information about the collection of a semen analysis. The study coordinator will give you a laboratory form including instructions as well as a collection cup for you to take to *[insert institution laboratory]* . You may also have the option of collecting the sample at home and bringing the sample to the medical center for testing. You will also be asked to sign an authorization of medical release form. This form will allow the study coordinator to receive your semen analysis results.

You will also be required to complete a medical history questionnaire. This questionnaire will ask you questions about your medical health, infertility history, demographic information, and family history. You will be given 5 questionnaires to complete. A Medical Outcomes Survey (Prime MD-PHQ) and the Short Form-36 (SF-36) will assess your daily activities. FertiQol will assess how your infertility affects your thoughts and feelings. The Sleep Habits Survey will assess the quality of your sleep. The

International Index of Erectile Function survey (IIEF) will assess your sexual function. You will be free to skip any questions that you would prefer not to answer.

As part of the inclusion criteria for participation in this study, intercourse must take place at least 2-3x's a week for the 20 week study period. Both you and your partner must agree to this requirement.

For the collection of the semen analysis test, it is important to not have sex or masturbate for 48 hours prior to collecting your sample.

Collection of sample at the *[insert institution name]*

[insert site specific semen analysis procedure]

Collection of sample at home

If the specimen is collected at home, follow the same instructions above and:

1. Bring the cup with you to the lab to drop off your sample.
2. The specimen should be kept warm (68-75 degrees Fahrenheit) during transportation by carrying it under clothing near the body, especially if it is cold out.
3. The specimen must be received to the lab within 30 minutes of collection.
4. DO NOT REFRIGERATE!

Once your specimen has been tested, the study coordinator will be given your results. Your results will be reviewed with the principal investigator of the study. You will be notified of your results. If the sperm concentration is greater than 14 million/mL, your partner/spouse will be eligible to participate in the main study. If the results of your semen analysis are abnormal, you will be provided with that information and referred to your physician for further follow-up. Your partner/spouse will be ineligible to participate in the main study at this time.

3. Discomforts and Risks:

There are no discomforts or risks associated with a semen analysis.

There is a risk of loss of confidentiality if your medical information or your identity are obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

4. Possible benefits:

a. Possible benefits to the participant:

You will be provided with your semen analysis results. Any abnormalities will be assessed by the principal investigator and followed through by your physician. There is no guarantee that you will benefit from being in this research.

b. Possible benefits to others:

The results of your semen analysis will determine eligibility for your partner/spouse to participate in the main study.

5. Other Options that Could be Used Instead of this Research:

You do not have to provide a semen analysis for testing. However, if you decline to do so, your partner/spouse will not be eligible to participate in the main study.

6. Time Duration of the Procedures and Study:

Participation in this study does not require any additional time on your part.

7. Statement of Confidentiality:

a. Privacy and confidentiality measures:

Your records that are used in the research at *[insert institution name]* will include your name, date of birth, medical record number and the date of your collection and will be kept in a secured area in a locked file cabinet within your partner/spouses research records for the main study.

To help protect your privacy, a Certificate of Confidentiality was obtained from the federal government. This Certificate means that the researchers cannot be forced (for example by court subpoena) to share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the U.S. government that is used for checking or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate, however, does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. This means that you and your family should actively protect your own privacy.

You should know that we may provide information to your health care providers if we suspect that you may harm yourself or others. We will not release any information collected as part of the research regarding use of illicit drugs and testing for drugs done on samples collected for the research.

In the event of any publication or presentation resulting from this research, no personally identifiable information will be shared.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

b. The use of private health information:

If you give your consent, health information about you will be collected for this research. Health information is protected by law as explained in the *[insert institution name]* Privacy Notice. If you have not received this notice, please request a copy from the researcher. At *[insert institution name]* your information will only be used or shared as

explained in this consent form or when required by law. However, some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information and may share it without your permission.

If you do not want us to use your protected health information, you may not participate in this research.

Your permission for the use, storage, and sharing of your identifiable health information will be kept indefinitely. Any research information in your medical record will be kept indefinitely.

If you choose to participate, you are free to withdraw your permission for the use and sharing of your health information at any time. You must do this in writing. Write to *[insert name of principal investigator]* and let him know that you are withdrawing from the research study. His mailing address is:

[insert contact information of principal investigator]

If you withdraw your permission:

- We will no longer use or share medical information about you for this research study, except when the law allows us to do so.
- We are unable to take back anything we have already done or any information we have already shared with your permission.
- We may continue using and sharing the information obtained prior to your withdrawal if it is necessary for the soundness of the overall research.
- We will keep our records of the care that we provided to you as long as the law requires.

The research team may use the following sources of health information:

- Semen analysis results
- Past medical history

Representatives of the following people/groups within *[insert institution name]* may use your health information and share it with other specific groups in connection with this research.

- The principal investigator, *[insert name of principal investigator]*
- The *[insert institution name]* Institutional Review Board
- The *[insert institution name]* Human Subjects Protection Office
- The research team and study coordinators
- The andrology laboratory staff
- The *[insert institution name]* Financial Analyst for Clinical Research

The above people/groups may share your health information with the following people/groups outside *[insert institution name]* for their use in connection with this research study. These groups, while monitoring the research study, may also review and/or copy your original *[insert institution name]* records.

- The Office of Human Research Protections in the U.S. Department of Health and Human Services
- Food and Drug Administration
- Yale University who represents the data collection center for this study
- Reproductive Medicine Network of The Eunice Kennedy Shriver National Institute of Child Health and Human Development

8. Costs for Participation:

[*insert site specific covered costs or non-covered services for semen analysis]*

9. Compensation for Participation:

You will not receive any compensation for being in this research study.

10. Research Funding:

The institution and investigators are receiving a grant from the National Institute of Health to support the research done in the main study.

11. Voluntary Participation:

Taking part in this research study is voluntary. If you choose to take part in this research, your major responsibilities will include:

-providing accurate past medical history information
-providing permission for the semen analysis results to be used in the study
-providing a semen analysis sample for testing
-following appropriate instructions for the collection of your sample

You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide not to participate, or if you decide to stop taking part in the research at a later date, your partner/spouse will not be able to participate in the main study.

12. Contact Information for Questions or Concerns:

You have the right to ask any questions you may have about this research. If you have questions, complaints or concerns or believe you may have developed an injury related to this research, contact *[insert name of principal investigator]* at xxx-xxx-xxxx.

If you have questions regarding your rights as a research participant or you have concerns or general questions about the research or about your privacy and the use of your personal health information, contact the research protection advocate in the *[insert institution name]* Human Subjects Protection Office at xxx-xxx-xxxx. You may also call this number if you cannot reach the research team or wish to talk to someone else.

For more information about participation in a research study and about the Institutional Review Board (IRB), a group of people who review the research to protect your rights, please visit the *[insert institution name]* IRB's Web site at *[insert website address]*.. Included on this web site, under the heading "Participant Info", you can access federal regulations and information about the protection of human research participants. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (xxx) xxx-xxxx.

Signature and Consent/Permission to be in the Research

Before making the decision regarding enrollment in this research you should have:

- Discussed this study with an investigator
- Reviewed the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Participant: By signing this consent form, you indicate that you are voluntarily choosing to take part in this research.

_____	_____	_____	_____
Signature of Participant	Date	Time	Printed Name

Person Explaining the Research: Your signature below means that you have explained the research to the participant and have answered any questions he has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

25 Appendix O: Investigator Signature of Agreement

Investigator Signature of Agreement

The Eunice Kennedy Shriver National Institute of Child Health and Human Development
Reproductive Medicine Network

Title: Pregnancy in Polycystic Ovary Syndrome II (PPCOS II):
A 25 Week Double-Blind, Randomized Trial of Clomiphene Citrate and Letrozole for the Treatment of Infertility in Women with Polycystic Ovary Syndrome

Version: 9.0

Principal Investigator:

I, *[Insert PI's name]*, the Principal Investigator for *[Insert Institute Name]*, hereby certify that I have read and agree to conduct this study in accordance with this protocol on behalf of all RMN Investigators and research staff from my site.

_____ _____

Signature Date

26 Appendix P: DSMB Charter

PREGNANCY IN POLYCYSTIC OVARY SYNDROME II (PPCOS II): A 20 WEEK DOUBLE-BLIND RANDOMIZED TRIAL OF CLOMIPHENE CITRATE AND LETROZOLE FOR THE TREATMENT OF INFERTILITY IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

DATA AND SAFETY MONITORING BOARD (DSMB) CHARTER

1. Purpose and Responsibilities of the DSMB

The members of the Data and Safety Monitoring Board (DSMB) identified in this Charter for the PPCOS II study are responsible for safeguarding the interests of study participants, assessing the safety and efficacy of all study procedures, and shall monitor the overall conduct of the PPCOS II trial. This Committee will serve as an independent advisory group to the Director of NICHD, and is required to provide recommendations about starting, continuing, and stopping the PPCOS II study.

This Committee is responsible for identifying mechanisms to complete various tasks that will impact the safety and efficacy of all study procedures, and overall conduct. The table below identifies the key areas where oversight is necessary and the ways in which the Committee for the PPCOS II study will complete those tasks.

Basic Responsibility of DSMB	Method DSMB for PPCOS II will use to complete task
Familiarize themselves with the study protocol	· Review study protocols and informed consent forms.
Monitor adverse events	· Adverse Event: Review quarterly progress reports prepared by the DCC on behalf of RMN. · Serious Adverse Events: Review report submitted by the DCC on behalf of RMN within one week of the event if life threatening or fatal, or within two weeks otherwise. The DSMB will submit a report of their review to the NICHD Committee Coordinator within 7 business days if the SAE is life threatening or fatal, or within two weeks otherwise.
Monitor data quality	· Conduct interim evaluations of the data.
Oversee participant recruitment and enrollment	· Review interim progress reports prepared by the DCC on behalf of RMN.
Develop an understanding of the Study's risks and benefits	· Review study protocols and related literatures. · Review interim reports of subject accrual and outcome measures provided by the DCC. · Assess the need to perform further in-depth evaluation of the benefits and risks of the study after reviewing each report.
Ensure the proper reporting occurs	· Review and approve the meeting and reporting schedule listed in Sections 5 and 7 of this DSMB charter.

2. Contacts

NICHD
Louis DePaolo, PhD, Program Officer
Charisee Lamar, PhD, Committee Coordinator
Esther Eisenberg, MD, Project Scientist

Data Coordination Center (DCC)
Heping Zhang, PhD, DCC Principal Investigator
Meizhuo Zhang, PhD, DCC Project Director
Sui Tsang, DCC Data Manager

Lead Investigator(s)
Richard S. Legro, MD

The Data Manager at the DCC will prepare the DSMB reports. The DCC Project Director will review all DSMB reports prior to submission to the DSMB. The DCC Data Manager will not be blind to treatment condition.

3. DSMB Members, Organizational Chart, & Communications

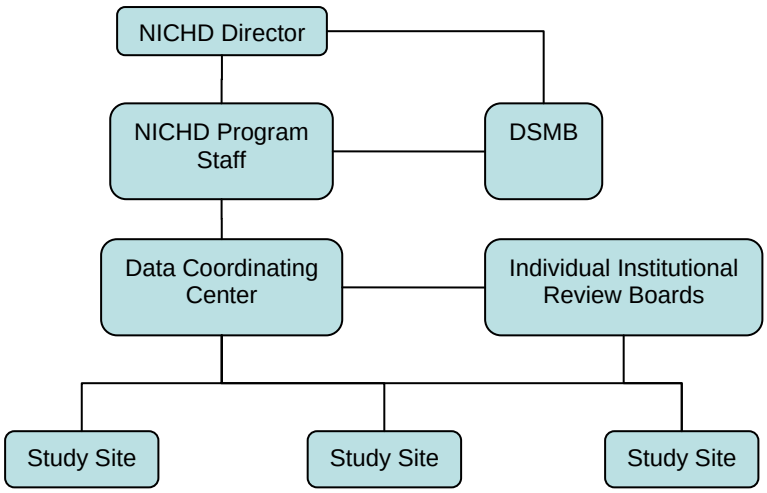
Members
The DSMB for the PPCOS II study is comprised of the members listed in the table below. In addition, their high level roles and responsibilities are identified in the table.

Name of Member	Role on DSMB	High Level Responsibilities
Robert Rebar, MD	Chair of DSMB Voting member	· Chair the DSMB discussion and prepare written recommendations to NICHD. · Ensure the safety of study subjects, the integrity of the research data. · Provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN. · Advises on research design issues, data quality and analysis, and research participant protection for each prospective and on-going study.
Rev. Phillip Cato, PhD	Voting member	· Ensure the safety of study subjects, the integrity of the research data. · Provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN. · Advises on research design issues, data quality and analysis, and research participant protection for each prospective and on-going study.
Vanja Dukic, PhD	Voting member	
Vivian Lewis, MD	Voting member	
Peter Schlegel, MD	Voting member	
Frank Witter, MD	Voting member	

Only Voting members for this DSMB may attend closed sessions for this Committee. In addition, only Voting members will have access to unblinded data points for this Committee.

Organizational Chart

The following diagram illustrates the relationship between the DSMB and other entities in the PPCOS II study.



Communication

Communication for members of this DSMB will be through the NICHD Program Office and, as approved by NICHD, the Data Coordination Center (DCC). Investigators from the PPCOS II study will not communicate directly with DSMB members about the study, except when making presentations or responding to questions at DSMB meetings or during scheduled conference calls.

4. Conflict of Interest and Compensation

It is extremely important that all members of the DSMB state any real or apparent conflicts of interests at the onset of the study. Members of the DSMB shall read the NICHD Clinical Research Guidance Document regarding Conflict of Interest and provide their signed summary of any COI for the study, at its onset, to the NICHD Committee Coordinator, Dr. Charisee Lamar. A table summarizing any COI within the DSMB is provided in the Appendix.

Prior to each meeting, all members of the RMN DSMB will have an opportunity to state whether they have developed any new conflicts of interest since the meeting. As a new COI is identified it must be documented in the table in the Appendix and a new signed summary of the COI should be provided to the NICHD Committee Coordinator. The Coordinator will forward the COI documentation to the DCC for record-keeping purposes.

If a new conflict is reported, the Coordinator and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion.

All DSMB members will be compensated for their role in supporting the committee. Compensation will include an honorarium for meeting attendance and any travel costs.

5. Meeting Schedule

DSMB meetings will be conducted quarterly. However, the DSMB may hold a meeting at any time in accordance with their mission. The NICHD Committee Coordinator will notify the DCC of any change in schedule.

6. Blinding

All summaries for DSMB reports will be presented in a blinded fashion, unless specified by the DSMB Chair.

7. Report Schedule and Content

The type of reports (full or brief) is indicated below, followed by a description of the contents of each type.

DSMB Report	Report Submission Date	Type of Report
1.	March 16th, 2009	Brief
2.	June 15th, 2009	Brief
3.	September 15th, 2009	Brief
4.	December 15th, 2009	**Full**
5.	March 15th, 2010	Brief
6.	June 15th, 2010	**Full**
7.	September 15th, 2010	Brief
8.	December 15th, 2010	**Full**
9.	March 15th, 2011	Brief
10.	June 15th, 2011	**Full**
11.	September 15th, 2011	Brief
12.	December 15th, 2011	**Full**
13.	March 15th, 2012	Brief
14.	June 15th, 2012	**Full**
15.	September 17th, 2012	Brief
16.	December 17th, 2012	**Full**

Brief DSMB reports will include the following summaries:

- overall actual versus projected enrollment accrual
- overall randomization update
- overall study drop-out rate
- serious adverse events
- primary outcome measures update

Full DSMB reports will include the following summaries:

- recruitment update (number screened) overall and by site
- enrollment update (enrolled defined as randomized to a treatment) overall and by site
- accrual status including actual enrollment compared to projections overall and by site
- randomization update (i.e., number assigned to each treatment arm)
- study drop-out rate for enrolled patients (number, reason, time point) overall and by site)
- pre-specified subset of baseline demographic data for enrolled patients
- safety data, adverse events, and serious adverse events
- number of case report forms expected
- number/percentage of expected case report forms received – overall and by site
- number of case report forms that are query clean
- primary outcome measures update

8. Efficacy Outcome Summary

We propose not to do an interim analysis. An interim analysis was planned in the initial PPCOS study, but the majority of subjects had been randomized by the time enough outcome data were accumulated to perform the interim analysis, and it was skipped. A similar scenario is anticipated in this study.

References

NIH Policy for Data and Safety Monitoring
http://grants.nih.gov/grants/guide/notice-files/NOT98-084.html
Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-supported Multi-center Clinical Trials
http://grants.nih.gov/grants/guide/notice-files/not99-107.html